Université de Montpellier

Ecole Doctorale CBS2

(Sciences Chimiques et Biologiques pour la Santé)

Habilitation à Diriger des Recherches

Approches intégrées en santé mondiale : des recherches multidisciplinaires en écologie, épidémiologie et sciences sociales pour améliorer la santé des populations vulnérables

Dossier de candidature

Andrés Garchitorena Garcia

UMR MIVEGEC (IRD 224 – CNRS 5290 – UM)

« Maladies Infectieuses et Vecteurs : Ecologie, Génétique, Evolution et Contrôle »

Date de soutenance :
19 octobre 2022

Jury :
Mme FLORENCE FOURNET, Présidente du jury, Directeur de recherche
M. JULIEN CAPPELLE, Membre du jury, Cadre scientifique des EPIC
Mme ANNABEL DESGRÉES DU LOU, Membre du jury, Directeur de recherche
M. SIMON CAUCHEMEZ, Rapporteur, Directeur de recherche
M. JEAN GAUDART, Rapporteur, Professeur des univ - praticien hosp.

Declaration d'intégrité scientifique

Je déclare avoir respecté, dans la conception et la rédaction de ce mémoire d'HDR, les valeurs et principes d'intégrité scientifique destinés à garantir le caractère honnête et scientifiquement rigoureux de tout travail de recherche, visés à l'article L.211-2 du Code de la recherche et énoncés par la Charte nationale de déontologie des métiers de la recherche et la Charte d'intégrité scientifique de l'Université de Montpellier. Je m'engage à les promouvoir dans le cadre de mes activités futures d'encadrement de recherche.

Table des matières

1. Curriculum Vitae

PERSONAL INFORMATION

Family name, First name: Garchitorena Garcia, Andrés

Researcher unique identifier: ORCID 0000-0001-6225-5226

Date of birth: June 23rd 1986

Nationality: Spanish

Status: Married, 1 child

PROFESSIONAL INFORMATION

CRCN - Institut de Recherche pour le Développement
MIVEGEC (IRD 224-CNRS 5290-UM)
IRD Délégation Régionale Occitanie
911, av. Agropolis BP 64501
34394 Montpellier Cedex 5
FRANCE
phone: +33 (0) 4 67 41 61 71
www.mivegec.ird.fr/

Languages: Spanish, French, English.

- **EDUCATION**

2011-2014	PhD in Microbiology & Parasitology. Title: Infectious Diseases, Ecosystems and Poverty: the Case of Buruli Ulcer in Cameroon Doctoral School on Integrated Systems in Biology, Agronomy, Geosciences, Hydrosciences and Environment (SIBAGHE). University of Montpellier 2, France PhD Supervisors: Jean Francois Guégan & Benjamin Roche
2011-2014	Complementary doctoral training in Public Health French Doctoral Network in Public Health, France
2009-2011	European Master in Public Health ("Europubhealth"), environmental health track. M1: Andalusian School of Public Health, Spain. M2: French School of Public Health, France
2004-2009	Doctor of Veterinary Medicine School of Veterinary Medicine. "Complutense" University of Madrid, Spain

- **CURRENT POSITIONS**

2021 –	Interim Director Représentation de l'IRD et du MNHN à Madagascar
2017 –	Research Scientist (CRCN) MIVEGEC, Institut de Recherche pour le Développement, France
2019 –	Associate Scientific Director NGO PIVOT, Madagascar

- **PREVIOUS POSITIONS**

2015 – 2017	Postdoctoral research fellow Department of Global Health and Social Medicine, Harvard Medical School, USA
2015 – 2017	Research Manager NGO PIVOT, Madagascar

- **FELLOWSHIPS AND AWARDS**

2011 – 2014 PhD doctoral fellowship (~100,000 €)
French School of Public Health, France
2009 – 2011 Graduate scholarship to pursue a Master program (42,000 €)
La Caixa Foundation, Spain. Academic Merit.
2004 – 2006 Undergraduate scholarship for students with academic excellence (10,000 €)
Comunidad de Madrid and Ministry of Education, Spain. Academic Merit.

- **REVIEWING ACTIVITIES**

2015 – Ad hoc reviewer for The Lancet Infectious Diseases, The Lancet Planetary Health, Ecology Letters, elife, PLoS Neglected Tropical diseases, BMJ Global Health, Scientific Reports, Infectious Diseases of Poverty, Parasites & Vectors, Virulence, BMJ Open, EcoHealth, BMC Public Health, International Journal of Health Geographics, HRB Open Research.
2020 Referee for the UK Medical Research Council (African Research Leader Scheme).

- **MEMBERSHIPS**

2020 – Advisory Board Member, Network "*PLAHNET-Planetary Health Network of Young Professionals*"
2017– 2019 Member. Working group. National Center for Ecological Analysis and Synthesis (NCEAS) and Science for Nature & People Partnership (SNAP) group "Ecological levels for health"

- **CURRENT PROJECTS**

2022-2025 **"***PREventing ZOonotic Diseases Emergence (PREZODE) – AfriCam Project – Madagascar Pilot"*
Role: co-PI. Budget: 1,800,000 € (total 10M€ for 5 countries). Funder: AFD, France
2022-2024 *"LSM: Assessing the effectiveness of bacterial larvicides on malaria prevalence and incidence in two districts of Madagascar"*
Role: coinvestigator. Budget: 340,000 €. Funder: USAID-PMI, United States
2021-2023 **"***Malaria remote populations (MRP): scaling tools for fine-scale geographic accessibility modelling in South Eastern Madagascar"*
Role: PI. Budget: 64,000 €. Funder: USAID-PMI, United States
2019-2023 *"SMALLER: Surveillance and control of malaria at the local level using e-health platforms"*
Role: PI. Budget: 229,000 €. Funder: ANR, France
2019-2023 *« CCM-malaria: Assessing the feasibility and effectiveness of community case management of malaria for all ages in Madagascar »*
Role: co-PI. Budget: 850,000 €. Funder: USAID-PMI, United States
2014-2023 *« I-HOPE: Ifanadiana Health Outcomes and Prosperity evaluation »*
Role: co-PI. Budget: 450,000 €. Funder: Herrnstein family foundation & NGO Pivot
2021-2022 *"SAY IHOPE: Serological Analysis of clinically relevant diseases in the IHOPE cohort"*
Role: co-PI. Budget: 100,000 €. Funder: NGO Pivot
2021-2022 *"PHDI: Population impact, Health geography and Disease eco-epidemiology in Ifanadiana"*
Role: PI. Budget: 20,000 €. Funder: NGO Pivot

2. Publications and communications

List of publications

At the beginning of April 2022, I have 34 peer reviewed articles (47% of which as first or last author), 4 contributions to books or book chapters, 2 conference abstracts published in peer reviewed journals, and 4 preprints in public repositories (not peer reviewed).

ORCID ID: 0000-0001-6225-5226

Total number of citations: 632 (h-index: 15; i10-index: 24)

(source google scholar: https://scholar.google.com/citations?user=2eqsHPMAAAAJ&hl)

Table 1. Summary of publications according to journal impact factor

Journal Impact Factor (categories)	Number of article publications	Number of article publications as first or last author	Impact Factor (range)
Over 10	1	1	11
Between 5 and 10	14	9	5,3-9,4
Between 3 and 5	14	5	3,1-4,4
Less than 3	5	1	2-2,8

List of peer reviewed articles (first author students I have supervised are underlined and in bold)

2022-1

- **Rajaonarifara** E, Bonds MH, Miller AC, Ihantamalala FA, Cordier L, Razafinjato B, Rafenoarimalala FH, Finnegan KE, Rakotonanahary RJL, Cowley G, Ratsimbazafy B, Razafimamonjy F, Randriamanambintsoa M, Raza-Fanomezanjanahary EM, Randrianambinina A, Metcalf CJ, Roche B, **Garchitorena A**. Impact of health system strengthening on delivery strategies to improve child immunisation coverage and inequalities in rural Madagascar. *BMJ Glob Heal*. **2022**;7(1):1–13.

2021-6

- Ihantamalala FA, Bonds MH, Randriamihaja M, Rakotonirina L, Herbreteau V, Révillion C, Rakotoarimanana S, Cowley G, Andriatiana TA, Mayfield A, Rich ML, Rakotonanahary RJL, Finnegan KE, Ramarson A, Razafinjato B, Ramiandrisoa B, Randrianambinina A, Cordier LF, **Garchitorena A**. Geographic barriers to establishing a successful hospital referral system in rural Madagascar. *BMJ Glob Heal*. **2021**;6(12).
- Sayre D, Steinhardt LC, Irinantenaina J, Dentinger C, Rasoanaivo TF, Kapesa L, Razafindrakoto J, Legrand A, Prada N, Gutman J, Lewis L, Mangahasimbola RT, Andriamananjara M, Ravaoarinosy AV, Ralemary N, **Garchitorena A**, Harimanana A. Baseline malaria prevalence and care-seeking behaviours in rural Madagascar prior to a trial to expand malaria community case management to all ages. *Malar J*. **2021**;20(1):1–13.
- **Garchitorena A**, Ihantamalala FA, Révillion C, Cordier LF, Randriamihaja M, Razafinjato B, Rafenoarivamalala FH, Finnegan KE, Andrianirinarison JC, Rakotonirina J, Herbreteau V, Bonds MH. Geographic barriers to achieving universal health coverage: evidence from rural Madagascar. *Health Policy Plan*. **2021**;00:1–12.

- Rakotonanahary RJL, Andriambolamanana H, Razafinjato B, Raza-Fanomezanjanahary EM, Ramanandraitsiory V, Ralaivavikoa F, Tsirinomen'ny Aina A, Rahajatiana L, Rakotonirina L, Haruna J, Cordier LF, Murray MB, Cowley G, Jordan D, Krasnow MA, Wright PC, Gillespie TR, Docherty M, Loyd T, Evans M V., Drake JM, Ngonghala CN, Rich ML, Popper SJ, Miller AC, Ihantamalala FA, Randrianambinina A, Ramiandrisoa B, Rakotozafy E, Rasolofomanana A, Rakotozafy G, Andriamahatana Vololoniaina MC, Andriamihaja B, **Garchitorena A**, Rakotonirina J, Mayfield A, Finnegan KE, Bonds MH. Integrating Health Systems and Science to Respond to COVID-19 in a Model District of Rural Madagascar. *Front Public Heal*. **2021**;9(July):1–10.
- **Evans M V.**, Bonds MH, Cordier LF, Drake JM, Ihantamalala F, Haruna J, Miller AC, Murdock CC, Randriamanambtsoa M, Raza-Fanomezanjanahary EM, Razafinjato BR, **Garchitorena A**. Socio-demographic, not environmental, risk factors explain fine-scale spatial patterns of diarrhoeal disease in Ifanadiana, rural Madagascar. *Proceedings Biol Sci*. **2021**;288(1946):20202501.
- **Hyde E**, Bonds MH, Ihantamalala FA, Miller AC, Cordier LF, Razafinjato B, Andriambolamanana H, Randriamanambintsoa M, Barry M, Andrianirinarison JC, Andriamananjara MN, **Garchitorena A.** Estimating the local spatio-temporal distribution of malaria from routine health information systems in areas of low health care access and reporting. *Int J Health Geogr*. **2021**;20(1):1–17.

2020-7

- Cordier LF, Kalaris K, Rakotonanahary RJL, Haruna J, Mayfield A, Marovavy L, Meg G, Tsirinomen A, Ratsimbazafy B, Loyd T, Ihantamalala F, **Garchitorena A**, Bonds MH, Finnegan KE, Aina T, Ratsimbazafy B, Razafinjato B, Loyd T. Networks of Care in Rural Madagascar for Achieving Universal Health Coverage in Ifanadiana District Networks of Care in Rural Madagascar for Achieving Universal Health Coverage in Ifanadiana District. *Heal Syst Reform*. **2020**;6(2).
- Roche B, Garchitorena A, Roiz D. The impact of lockdown strategies targeting age groups on the burden of COVID-19 in France. *Epidemics*. **2020**;33:100424.
- **Garchitorena A**, Miller AC, Cordier LF, Razanadrakato TR, Randriamanambintsoa M, Randriamihaja M, Razafinjato B, Finnegan KE, Haruna J, Rakotonirina L, Rakotozafy G, Raharimamonjy L, Atwood S, Murray MB, Rich M, Loyd T, Solofomalala GD, Bonds MH. District-level health system strengthening for universal health coverage : evidence from a longitudinal cohort study in rural Madagascar , 2014- 2018. *BMJ Glob Heal*. **2020**;5:e003647.
- Evans MV, **Garchitorena A**, Rakotonanahary RJL, Drake JM, Andriamihaja B, Rajaonarifara E, Ngonghala CN, Roche B, Bonds MH, Rakotonirina J. Reconciling model predictions with low reported cases of COVID-19 in Sub-Saharan Africa: insights from Madagascar. *Glob Health Action*. **2020**;13(1).
- Roche B, **Garchitorena A**, Guégan JF, Arnal A, Roiz D, Morand S, Zambrana-Torrelio C, Suzán G, Daszak P. Was the COVID-19 pandemic avoidable? A call for a "solution-oriented" approach in pathogen evolutionary ecology to prevent future outbreaks. *Ecol Lett.* **2020**;23(11):1557–60.
- Ihantamalala FA, Herbreteau V, Revillion C, Randriamihaja M, Commins J, Andreambeloson T, Rafenoarivamalala FH, Randrianambinina A, Cordier LF, Bonds MH, **Garchitorena A**. Improving geographical accessibility modeling for operational use by local health actors. *Int* J Health Geogr. **2020**;19(27).
- Miller AC, **Garchitorena A**, Rabemananjara F, Cordier L, Randriamanambintsoa M, Rabeza V, Razanadrakoto HTR, Rakoto Ramakasoa R, Ramahefarisontiana O, Ratsimbazafy BN, Ouenzar MA, Bonds MH, Ratsifandrihamanana L. Factors associated with risk of developmental delay in

preschool children in a setting with high rates of malnutrition: A cross-sectional analysis of data from the IHOPE study, Madagascar. *BMC Pediatr*. **2020**;20(1):1–11.

2019-1

- **Ezran C**, Bonds MH, Miller AC, Cordier LF, Haruna J, Mwanawabenea D, Randriamanambintsoa M, Razanadrakato R, Ouenzar MA, Murray M, **Garchitorena A**. Assessing trends in the content of maternal and child care following a health system strengthening initiative in rural Madagascar : A longitudinal cohort study. *PLoS Med*. **2019**;16(8):1–23.

2018-5

- **Garchitorena A**, Raza-Fanomezanjanahary EM, Mioramalala SA, Chesnais C, Ratsimbasoa CA, Ramarosata H, Bonds MH, Rabenantoandro H. Towards elimination of lymphatic filariasis in southeastern Madagascar: Successes and challenges for interrupting transmission. *PLoS Negl Trop Dis*. **2018**;12(9):e0006780.
- **Garchitorena A**, Miller AC, Cordier LF, Rabeza VR, Randriamanambintsoa M, Razanadrakato H-TR, Hall L, Gikic D, Haruna J, McCarty M, Randrianambinina A, Thomson DR, Atwood S, Rich ML, Murray MB, Ratsirarson J, Ouenzar MA, Bonds MH. Early changes in intervention coverage and mortality rates following the implementation of an integrated health system intervention in Madagascar. *BMJ Glob Heal*. **2018**;3(3):e000762.
- Miller AC, **Garchitorena A**, Rabeza V, Randriamanambintsoa M, Razanadrakato H-TR, Cordier L, Ouenzar MA, Murray MB, Thomson DR, Bonds MH. Cohort Profile: Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation (IHOPE). *Int J Epidemiol*. **2018**;0(0):1–7.
- Mccuskee S, **Garchitorena A**, Miller AC, Hall L, Ouenzar A, Rabeza VR, Ramananjato RH, Rahaniraka H, Randriamanambintsoa M, Barry M, Matthew H, Mccuskee S, Garchitorena A, Miller AC, Hall L, Ouenzar A, Rabeza VR, Ramananjato RH, Razanadrakato HR, Randriamanambintsoa M, Barry M, Bonds MH. Child malnutrition in Ifanadiana district, Madagascar : associated factors and timing of growth faltering ahead of a health system strengthening intervention. *Glob Health Action*. **2018**;11(1).
- Bonds MH, Ouenzar MA, **Garchitorena A**, Cordier LF, McCarty MG, Rich ML, Andriamihaja B, Haruna J, Farmer PE. Madagascar can build stronger health systems to fight plague and prevent the next epidemic. *PLoS Negl Trop Dis*. **2018**; 12(1): e0006131
  -

2017-4

- **Garchitorena A**, Miller AC, Cordier LF, Ramananjato R, Rabeza VR, Murray M, Cripps A, Hall L, Farmer P, Rich M, Orlan AV, Rabemampionona A, Rakotozafy G, Randriantsimaniry D, Gikic D, Bonds MH. In Madagascar, use of health care services increased when fees were removed: Lessons for universal health coverage. *Health Aff*. **2017**;36(8):1443–51.
- Miller AC, Ramananjato RH, **Garchitorena A**, Rabeza VR, Gikic D, Cripps A, Cordier L, Rahaniraka Razanadrakato H-T, Randriamanambintsoa M, Hall L, Murray M, Safara Razanavololo F, Rich ML, Bonds MH. Baseline population health conditions ahead of a health system strengthening program in rural Madagascar. *Glob Health Action*. **2017**;10(1):1329961.
- **Garchitorena A**, Sokolow S, Roche B, Ngonghala CN, Jocque M, Lund A, Barry M, Mordecai EA, Daily GC, Jones JH, Andrews JR, Bendavid E, Luby SP, LaBeaud A, Seetah K, Guégan J, Bonds M, De Leo G. Disease Ecology, Health and Environment: a framework to account for ecological and socio-

economic drivers in the control of neglected tropical diseases. *Philos Trans R Soc B Biol Sci*. **2017**;372(1722).

- Combe M, Velvin CJ, Morris A, **Garchitorena A**, Carolan K, Sanhueza D, Roche B, Couppié P, Guégan J-F, Gozlan RE. Global and local environmental changes as drivers of Buruli ulcer emergence. *Emerg Microbes Infect*. **2017**;6(e22)

2016-1

- García-Peña GE, **Garchitorena A**, Carolan K, Canard E, Prieur-Richard A, Suzán G, Mills JN, Roche B, Guégan J. Niche-based host extinction increases prevalence of an environmentally acquired pathogen. *Oikos*. **2016**;125(10).

2015-6

- **Garchitorena A**, Ngonghala CN, Guégan J-F, Texier G, Bellanger M, Bonds M, Roche B. Economic inequality caused by feedbacks between poverty and the dynamics of a rare tropical disease: The case of buruli ulcer in sub-Saharan Africa. *Proc R Soc B Biol Sci.* **2015**;282(1818).
- **Garchitorena A**, Ngonghala CN, Texier G, Landier J, Eyangoh S, Bonds MH, Guégan J-F, Roche8 B. Environmental transmission of Mycobacterium ulcerans drives dynamics of Buruli ulcer in endemic regions of Cameroon. *Nat Sci Reports*. **2015**;5(November):18055.
- **Garchitorena A**, Guégan J-F, Léger L, Eyangoh S, Marsollier L, Roche B. Mycobacterium ulcerans dynamics in aquatic ecosystems are driven by a complex interplay of abiotic and biotic factors. *Elife*. 2015;4:e07616.
- Rist CL, **Garchitorena A**, Ngonghala CN, Gillespie TR, Bonds MH. The Burden of Livestock Parasites on the Poor. Vol. 31, *Trends in Parasitology*. **2015**. p. 527–30.
- Rist CL, Ngonghala CN, **Garchitorena A**, Brook CE, Ramananjato R, Miller AC, Randrianarivelojosia M, Wright PC, Gillespie TR, Bonds MH. Modeling the burden of poultry disease on the rural poor in Madagascar. *One Heal*. **2015**;1:60-65.
- Landier J, Magny GC De, **Garchitorena A**, Guégan J, Gaudart J, Marsollier L, Gall PLPL, Giles-Vernick T, Eyangoh S, Fontanet A, Texier G, de Magny GC, Garchitorena A, Gu?gan J-F, Gaudart J, Marsollier L, Gall PLPL, Giles-Vernick T, Eyangoh S, Fontanet A, Texier G. Seasonal Patterns of Buruli Ulcer Incidence , Central Africa, 2002-2012. *Emerg Infect Dis*. **2015**;21(8):10–3.

2014-3

- **Garchitorena A**, Roche B, Kamgang R, Ossomba J, Babonneau J, Landier J, Fontanet A, Flahault A, Eyangoh S, Guégan J-F, Marsollier L, Guégan J-F, Marsollier L. Mycobacterium ulcerans Ecological Dynamics and Its Association with Freshwater Ecosystems and Aquatic Communities: Results from a 12-Month Environmental Survey in Cameroon. *PLoS Negl Trop Dis*. **2014**;8(5):e2879.
- Carolan K, **Garchitorena A**, García-Peña GE, Morris A, Landier J, Fontanet A, Le Gall P, Texier G, Marsollier L, Gozlan RE, Eyangoh S, Lo Seen D, Guégan J-F. Topography and Land Cover of Watersheds Predicts the Distribution of the Environmental Pathogen Mycobacterium ulcerans in Aquatic Insects. *PLoS Negl Trop Dis*. **2014**;8(11).
- Carolan K, Ebong SMÀ, **Garchitorena A**, Landier J, Sanhueza D, Texier G, Marsollier L, Gall PL, Guégan J-F, Seen DL. Ecological niche modelling of Hemipteran insects in Cameroon; The paradox of a vector-borne transmission for Mycobacterium ulcerans, the causative agent of Buruli ulcer. *Int J Health Geogr*. **2014**;13(1).

List of books and book chapters

- **Garchitorena A**, Murray MB, Hedt-Gauthier B, Farmer PE, Bonds MH. Reducing the knowledge gap in global health delivery: contributions and limitations of randomized controlled trials. In: Randomized Control Trials in the Field of Development. Oxford: *Oxford University Press*; **2020**. p. 425.
- **Garchitorena A**, Bonds MH, Guégan J, Roche B. Interactions between ecological and socio-economic drivers of Buruli ulcer burden in Sub-Saharan Africa : opportunities for an improved control. In: Ecology and Evolution of Infectious Disease: pathogen control and public health management in low-income countries. 2018th ed. *Oxford University Press*; **2018**. p. 217–35.
- Bonds MH, **Garchitorena A**, Farmer PE, Murray MB. Ecology of poverty, disease and health care delivery: lessons for planetary health. In: Ecology and Evolution of Infectious Disease: pathogen control and public health management in low-income countries. *Oxford University Press*; **2018**. p. 285–96.
- WHO French Healthy Cities Network. Pour un habitat favorable à la santé. Les contributions des villes. *Presses de l'EHESP*; **2011**. (co-editor and co-author of several chapters)

List of conference abstracts published in peer reviewed journals

- **Garchitorena A**, Bonds MH, Ngonghala CN, Guégan J-F, Roche B. Modelling ecological and socioeconomic feedbacks of Buruli ulcer in sub-Saharan Africa: results from a field study in Cameroon. *Lancet*. **2017** May 1;389:S9.
- De Leo GA, Sokolow SH, **Garchitorena A**, Ngonghala CN, Lund A, Barry M, Burke KS, Mordecai EA, Daily GC, Jones JH, Andrews JR, Bendavid E, Luby SP, LaBeaud AD, Seetah K, Guégan J-F, Lafferty K, Wood CL, Jones IJ, Bonds MH. A novel framework to account for ecological drivers in the control and elimination of environmentally transmitted disease: a modelling study. *Lancet*. **2017** May 1;389:S5.

List of preprints in public repositories

- Razafinjato B, Rakotonirina L, Andriantahina JB, Cordier LF, Andriamihaja R, Rasoarivao A, Andrianomenjanahary M, Marovavy L, Hanitriniaina F, Mayfield A, Palazuelos D, Ihantamalala F, Rakotonanahary RJL, Miller A, **Garchitorena A**, McCarty MG, Bonds MH, Finnegan KE. Evaluation of a novel approach to community health care delivery in Ifanadiana District, Madagascar. *medRxiv*. **2020**.
- Finnegan KE, Haruna J, Cordier LF, Razafinjato B, Rakotonirina L, Randrianambinina A, Rakotozafy E, Andriamihaja B, **Garchitorena A**, Bonds MH, Ouenzar MA. Rapid response to a measles outbreak in Ifanadiana District , Madagascar. *medRxiv*. **2020**.
- Garchitorena A, Gruson H, Cazelles B, Roche B. Quantifying the efficiency of non-pharmaceutical interventions against SARS-COV-2 transmission in Europe. *medRxiv*. **2020**.
- Bonds MH, **Garchitorena A**, Cordier L, Miller AC, McCarty M, Adriamihaja B, Ratsirarson J, Randrianambinina A, Rabeza VR, Finnegan K, Gillespie T, Wright PA, Farmer PE, Loyd T, Murra M, Herrnstein RM, Herrnstein JR, Gikic D, Ouenzar MA, Hall L, Rich ML. Advancing a Science of Sustaining Health: A New Platform for a Model District in Madagascar. *bioRxiv*. **2017**.

Scientific conferences and seminars

2022-1

- Geographic Barriers to Achieving Universal Health Coverage: evidence from rural Madagascar. Webinaires QuanTIM. Online. 2022. Invited speaker

2021-3

- Estimation de la distribution spatio-temporelle locale du paludisme à partir des systèmes de surveillance passive dans les zones avec faible accès aux soins et rapportage. 3ème Conférence scientifique sur le Paludisme. Antananarivo, Madagascar. 2021. Oral presentation.
- Evaluation de la faisabilité et de l'efficacité de l'extension de la prise en charge communautaire du paludisme pour tous les âges. USAID's Madagascar Population, Health and Nutrition quarterly meeting. Antananarivo, Madagascar. 2021. Invited speaker
- The ecology of health care delivery: insights for local disease control. Seminaires MIVEGEC. Online. 2021. Invited speaker

2020-6

- COVID-19 modelling and health system strengthening in Madagascar. IORA & Water Research Commission of South Africa, Research and Innovation sharing workshop, COVID-19 research and innovation programmes and projects implemented by IORA MS and DP. Online. 2020. Invited speaker.
- Challenges Humanity Face in the Anthropocene era through different lenses. Planetary Health Network of Health Professionals (PlaHNET). Planetary Health Webinar Series. Online. 2020. Invited speaker.
- Malaria prevalence and care seeking behaviors prior to a pilot expanding malaria community case management to older ages in Farafangana, Madagascar, 2019. ASTMH Annual meeting. Online. 2020. Co-author, poster presentation.
- Improving geographical accessibility modeling for operational use by local health actors. 6th Global Symposium on Health Systems Research. Online. 2020. Co-author, poster presentation.
- Modélisation de COVID-19 et renforcement de systèmes de santé à Madagascar. Journée des acteurs Français en santé, Ambassade de France Madagascar. Antananarivo, Madagascar. 2020. Oral presentation.
- Surveillance et contrôle du paludisme au niveau local. Roll Back Malaria Madagascar working group. Antananarivo, Madagascar. 2020. Oral presentation.

2019-6

- Évaluation des tendances du contenu des soins maternels et infantiles suite à une initiative de renforcement du système de santé à Ifanadiana. 2ème Journée scientifique sur l'apport de la recherche au renforcement du système de santé à Madagascar. Antananarivo, Madagascar. 2019. Oral presentation.
- Augmentation de l'utilisation des services de santé à Ifanadiana suite à la suppression des paiements de poche: leçons pour la Couverture Sanitaire Universelle. 2ème Journée scientifique sur l'apport de la recherche au renforcement du système de santé à Madagascar. Antananarivo, Madagascar. 2019. Oral presentation.
- Changements précoces dans la couverture des soins et les taux de mortalité suite à une intervention de renforcement du système de santé à Ifanadiana. 2ème Journée scientifique sur l'apport de la

recherche au renforcement du système de santé à Madagascar. Antananarivo, Madagascar. 2019. Oral presentation.
- Déterminants socio-économiques et environnementaux des maladies tropicales négligées. 2ème Congrès de recherche en Santé Publique de l'Océan Indien du CHU de La Réunion. La Réunion, France. 2019. Invited speaker.
- Modélisation de l'accessibilité géographique aux soins suite à un programme de renforcement du système de santé à Ifanadiana, Madagascar. 2ème Congrès de recherche en Santé Publique de l'Océan Indien du CHU de La Réunion. La Réunion, France. 2019. Co-author, poster presentation (best poster).
- Round table: Methods, practices, narratives and ethics: different perspectives on randomized experiments in developing countries. AFD seminar "Randomized Control Trials in Development: the Gold Standard Revisited". Paris, France. 2019. Invited speaker.

2018-2

- Building evidence from the ground up: service at the core of PIVOT research. A crucible for Planetary Health, Centre ValBio (Madagascar). Antananarivo, Madagascar. 2018. Oral presentation.
- Round table : La santé pour toutes et tous : enjeux et défis pour Madagascar. 70 ans de l'IRD à Madagascar. Antananarivo, Madagascar. 2018. Invited speaker.

2017-2

- Modelling ecological and socioeconomic feedbacks of Buruli ulcer in sub-Saharan Africa: results from a field study in Cameroon. Planetary Health/GeoHealth Annual Meeting. Boston, USA. 2017. Poster presentation
- A novel framework to account for ecological drivers in the control and elimination of environmentally transmitted disease: a modelling study. Planetary Health/GeoHealth Annual Meeting. Boston, USA. 2017. Poster presentation

2016-1

- Evaluation de l'impact de la réduction des barrières d'accès aux soins dans le district d'Ifanadiana, Madagascar. 1er Colloque francophone d'anthropologie de la santé à Madagascar. Antananarivo, Madagascar. 2016. Oral presentation

2015-2

- Environmental transmission of *Mycobacterium ulcerans* drives dynamics of Buruli ulcer in endemic regions of Cameroon. 13th EEID Conference. Athens, USA. 2015. Oral presentation
- Infectious diseases, ecosystems and poverty: the case of Buruli ulcer in Cameroon. Ecology of poverty and economic development working group, Marseille, France. 2015. Oral presentation

2014-2

- The impact of abiotic parameters and host community structure on a multi-host pathogen: the case of *Mycobacterium ulcerans* in Cameroon. 99th ESA Annual Meeting. Sacramento, USA. 2014. Oral presentation
- The impact of freshwater ecosystems and aquatic communities on *Mycobacterium ulcerans* ecological dynamics. 9th Louis Pasteur Conference, Emerging Infectious Diseases. Paris, France. 2014. Oral presentation

2013-1

- The ecology and transmission of *Mycobacterium ulcerans* in Cameroon. French Doctoral Network of Public Health. Paris, France. 2013. Oral presentation

2011-1

- Housing and Health: The experience of the WHO French Healthy Cities Network. Nantes Public Health Department. Nantes, France. 2011. Oral presentation

Outreach activities

Documentaries

- La fabrique des pandémies. Préserver la biodiversité c'est protéger notre santé. M2R Films, starring Juliette Binoche. In production. 2022. https://m2rfilms.com/espace-membres/fabrique-des-pandemies

Blogs and institutional communications

- Universal health coverage policies may fail to ensure the provision of primary care for all without a stronger commitment to community health. Health Policy and Planning Debated. 2021. https://blogs.lshtm.ac.uk/hppdebated/2021/08/23/
- La modélisation de l'accessibilité géographique est opérationnelle pour des acteurs locaux de la santé : exemple dans le district d'Ifanadiana. Communication IRD. 2021. https://en.ird.fr/node/8749
- Mieux réagir face aux épidémies. Dossier : Les maladies infectieuses dans le viseur des scientifiques de la région. Communication IRD. 2020. https://www.ird.fr/dossier-les-maladies-infectieuses-dans-le-viseur-des-scientifiques-de-la-region
- Voices from the field #2: Our Data & Research on the Spread of COVID-19. NGO Pivot. 2020. https://www.youtube.com/watch?v=L848qhy-rzU

Media interviews

- Article interview. Flesh-eating ulcer spreading in Australia, and reasons remain a mystery. CNN (April 16, 2018). https://edition.cnn.com/2018/04/16/health/australia-flesh-eating-ulcer-intl/index.html

3. Teaching activities and student supervision

Teaching activities

2019 – 2022 Visiting lecturer – Introduction to Planetary Health. M1, Master in Public Health. French School of Public Health (EHESP). Paris, France. Workload: 14h of teaching per year

2021 Instructor – Correlation and Linear Regression in Epidemiology. Course on basic statistical methods. Institut Pasteur Madagascar (IPM). Antananarivo, Madagascar. Workload: 2h of teaching.

2016 – 2020 Visiting lecturer – Statistical Modelling. Workshop "E2M2: Ecological and Epidemiological Modelling in Madagascar". Centre ValBio. Ranomafana, Madagascar. Workload: 10h of teaching and 10 of student mentorship per year.

2019 Instructor – Course « Introduction aux statistiques avec le logiciel R ». ONG PIVOT. Ranomafana, Madagascar. Workload: 10h of teaching and organization.

2018 Instructor – Cartoparty of Ifanadiana District. Université de Fianarantsoa, Ecole Management et Innovation Technologique (EMIT). Fianarantsoa, Madagascar. Workload: 2h of teaching and 6h of student mentorship.

2017 Visiting lecturer – Module "Global Environmental Changes and Planetary Health". M2, Master in Public Health. French School of Public Health (EHESP). Paris, France. Workload: 12 hours of teaching + module co-coordination with Helene Broutin (UMR MIVEGEC).

Student supervision

PhD students (2)

- Jean Marius RAKOTONDRAMANGA. Start date: September 2018 (ongoing). ED393, Sorbonne Université. Co-supervision with Benjamin Roche (UMR MIVEGEC).
- Elinambinina RAJOANARIFARA : Start date: September 2019 (ongoing). ED393, Sorbonne Université. Co-supervised with Benjamin Roche.

Master 2 students (7)

- Augustin RAKINGAMIAINA. Duration: March to July 2022 (ongoing). « Tendances spatio-temporelles de l'utilisation des soins de santé primaire dans le district de Farafangana, Madagascar ».Master en Systèmes d'Information, Géomatique et Décision. EMIT, Université de Fianarantsoa. Internship at IPM. Antananarivo, Madagascar.
- Judickaelle IRINANTENAINA. Duration: March to July 2022 (ongoing). « Déterminants du paludisme dans le district de Farafangana (Madagascar), 2019-2021 ». Master Sciences, Technologies, Santé, Mention Santé Publique. Université de Bordeaux – ISPED. Internship at IPM. Antananarivo, Madagascar.
- Alexandra CAGNIANT-ROUSSEAU. Duration: April to August 2021. « Déterminants d'accès aux soins primaires à Madagascar en 2019: cas du district de Farafangana ». Master Sciences, Technologies,

Santé, Mention Santé Publique. Université de Bordeaux – ISPED. Internship at IPM. Online mentorship.

- Tanjona Tahina ANDREAMBELOSON. Duration: February to July 2019. « L'apport de la géomatique pour comprendre les barrières d'accès aux soins de santé dans le district d'Ifanadiana ». Master en Systèmes d'Information, Géomatique et Décision. EMIT, Université de Fianarantsoa. Internship at Pivot. Ranomafana, Madagascar.
- Miadana Joëlle RAKOTOZAFINIRAINY. Duration: February to July 2019. « Modélisation de la dynamique spatio-temporelle du paludisme dans le District d'Ifanadiana ». Master en Systèmes d'Information, Géomatique et Décision. EMIT, Université de Fianarantsoa. Internship at Pivot. Ranomafana, Madagascar.
- Mauricianot RANDRIAMIHAJA. Duration: February to July 2019. « Estimation du temps de parcours aux soins de santé dans le District d'Ifanadiana ». Master en Systèmes d'Information, Géomatique et Décision. EMIT, Université de Fianarantsoa. Internship at Pivot. Ranomafana, Madagascar.
- Camille EZRAN. Duration: July to December 2017. "The impact of a health system strengthening initiative on the quality of healthcare in a rural district of Madagascar". Masters Degree in Health Policy. Department of Health Research and Policy, Stanford University School of Medicine. Internship at Pivot. Online mentorship.

Other international students (4)

- Elizabeth HYDE. Medical student (2018/2019). "Using healthcare access models to estimate the burden of malaria missed by routine surveillance in a rural area of Madagascar". Medical Scholars Program, Stanford University School of Medicine. Internship at Pivot. Ranomafana, Madagascar.
- Isabel JONES. PhD internship (2019). "Drivers of local malaria transmission in Ifanadiana District, Madagascar". Stanford University. Internship at Pivot. Ranomafana, Madagascar.
- Michelle EVANS. PhD internship (2019). "Drivers of zoonotic transmission of enteric pathogens and diarrheal disease risk in populations living at the edge of Ranomafana National Park". University of Georgia Athens. Internship at Pivot. Ranomafana, Madagascar.
- Sarah McCUSKEE. Medical student (2017). "Epidemiology and treatment of child malnutrition in Ifanadiana district, Madagascar". Medical Scholars Program, Stanford University School of Medicine. Internship at Pivot. Online mentorship.

Postdoctoral researchers (3)

- Michelle EVANS. Duration: March 2021 to March 2023 (ongoing). "Statistical and mathematical modelling of local malaria transmission in Ifanadiana District to optimize control". Co-supervision with Benjamin Roche. Funding: ANR.
- Tanjona RAMIADANTSOA. Duration: November 2020 to November 2021. "Mathematical modelling of covid-19 transmission". Co-supervision with Benjamin Roche. Funding: AFD.
- Felana A. IHANTAMALALA. Duration: January 2018 to January 2024 (ongoing). "Geography of health care access in Ifanadiana District, Madagascar". Funding: Pivot

4. Research contracts and management

Current projects

2022-2025 "*PREventing ZOonotic Diseases Emergence (PREZODE) – AfriCam Project – Madagascar Pilot"*

Role: co-PI (PI: Veronique Chevalier, CIRAD). Budget: 1,800,000 €. Funder: AFD, France

(*AfriCam Project budget is 10M€ for 5 countries; PIs Benjamin Roche & Marisa Peyre*).

2022-2024 *"LSM: Assessing the effectiveness of bacterial larvicides on malaria prevalence and incidence in two districts of Madagascar"*

Role: coinvestigator (PI Rila Ratovson, IPM). Budget: 340,000 €. Funder: USAID-PMI

2021-2023 "*MRP: Malaria remote populations. Scaling tools for fine-scale geographic accessibility modelling in South Eastern Madagascar"*

Role: PI. Budget: 64,000 €. Funder: USAID-PMI

2019-2023 *"SMALLER: Surveillance and control of malaria at the local level using e-health platforms"*

Role: PI. Budget: 229,000 €. Funder: ANR, France

2019-2023 *« CCM-malaria: Assessing the feasibility and effectiveness of community case management of malaria for all ages in Madagascar »*

Role: co-PI (co-PI Laura Steinhardt, CDC). Budget: 850,000 €. Funder: USAID-PMI

2014-2023 *« I-HOPE: Ifanadiana Health Outcomes and Prosperity evaluation »*

Role: co-PI (co-PI Ann Miller, Harvard). Budget: 450,000 €. Funder: Herrnstein family foundation & NGO Pivot

2021-2022 *"SAY IHOPE: Serological Analysis of clinically relevant diseases in the IHOPE cohort"*

Role: co-PI (co-PI Matthieu Schoenhals, IPM). Budget: 100,000 €. Funder: NGO Pivot

2021-2022 *"PHDI: Population impact, Health geography and Disease eco-epidemiology in Ifanadiana"*

Role: PI. Budget: 20,000 €. Funder: NGO Pivot

Previous projects

2018 *"MAGIE: Mobile technologies for geographical access to healthcare"*

Role: PI. Budget: 15,000 €. Funder: IRD-Coup de Pouce

2018 *"BEHAVIOR: Modelling of behaviour in pathogen transmission"*

Role: co-PI (PI Benjamin Roche, IRD). Budget: 10,000 €. Funder: CNRS-PEPS

Research management

Associate scientific director at the NGO Pivot (2019-present)

Since July 2019, I am Associate Scientific Director for the NGO Pivot. Pivot works in partnership with the Madagascar Ministry of Public Health in Ifanadiana district to strengthen the public health system and gradually achieve universal health coverage in the district. This NGO places particular emphasis on monitoring, evaluation and research to evaluate the evolution and impact of its interventions and achieve its goal of creating a model health district for the country. In my capacity as associate scientific director, I am responsible for a team of about 10 people based in Ifanadiana including doctoral students, post-docs, engineers, and data collection agents, who participate in the SMALLER, IHOPE, and PHDI projects, among others. I have also supported the establishment in 2020 of a new division within Pivot called Pivot Science, which formally acknowledges the importance of research as an accompaniment and driver of health systems strengthening implementation. The creation of Pivot Science allows us to create organisational systems (HR, admin, finance, etc.) that are better adapted for the conduct of research, as opposed to those necessary for programmatic implementation of healthcare activities. I also play a strategic role within the organization, helping set research priorities, supporting fundraising, informing programs on their impact over time, coordinating activities with other partners (IPM, INSTAT, etc.) and discussing research with the Ministry of Public Health.

Interim Director of IRD Madagascar (2021-present)

Since July 2021, I am the Interim Director ("Representant") of IRD in Madagascar. In the first six months, this was purely an administrative interim while the Director was on a mission or holidays (e.g. approving missions, expenses, etc.). Since January 2022 though, the position of Director has been vacant, so I have a much larger set of responsibilities. First, I am responsible for the headquarters of IRD in Madagascar, including a local team of about 10 people based at the "Representation" comprised of administrative, finance and communication assistants, domestic workers and drivers. Second, I am IRD's point person at the French Embassy in Madagascar, so I participate at monthly meetings with all French actors and I coordinate with the Embassy's cooperation service (SCAC) the organization and valorisation of multiple activities involving IRD and its partners. Third, I am the guarantor of the security of IRD and MNHN agents on mission in Madagascar (plus Maurice, Seychelles and Comoros), and as such I evaluate, validate and give recommendations for every mission taking place. Finally, I ensure the institutional and scientific representation of the IRD with the institutions and partners of Madagascar as well as with the French, European and international actors.

Research manager at the NGO Pivot (2015-2017)

From March 2015 to July 2017, I had the role of Research Manager for the NGO Pivot. My role as the NGO's first research manager (Pivot was founded one year prior) was double. First, I helped develop and implement the NGO's research program on the ground, coordinating all research projects while being the interlocutor with the Ministry of Public Health and other organizations for the dissemination of results. This included many management activities such as annual planning and budgeting, fundraising, and the follow-up of multiple research projects, both internal and external. In addition, in the early years of Pivot's creation, the NGO had little research capacity so we created a research committee that gave competitive grants ranging from 5,000 to 50,000 USD for international teams wishing to develop research projects that are consistent with Pivot's mission in Ifanadiana. Thus, I was the focal point of Pivot's research committee on the ground and I evaluated all the research proposals

submitted to the NGO, giving the necessary support in the field for the conduct of the accepted projects. I also participated in the local strengthening of research capacities, conducting training workshops in Ifanadiana (use of the R software for statistics, modelling of infectious diseases, etc.). Upon being hired by IRD in July 2017, I helped recruit my replacement as a research manager and I became Pivot's scientific advisor, doing many of the same activities, but progressively delegating most of the management tasks to the new manager in order to ensure a smooth transition on the ground.

Other activities

PREZODE – Focal Point for IRD in the Indian Ocean (2021-present)

PREventing ZOonotic Diseases Emergence (PREZODE) is an international initiative addressing challenges related to the prevention, surveillance, early detection and rapid response to risks of zoonotic pandemics. PREZODE was set up by three French research institutes–INRAE, CIRAD and IRD– in cooperation with several public and private research organisations from over 50 countries and international organisations including WHO, OIE, FAO and UNEP. Since the spring of 2021, I have been appointed PREZODE's focal point for IRD in the Indian Ocean. In this capacity, I have helped with the organization and facilitation of three online co-construction workshops gathering over 150 participants in the region. These workshops, which are aimed at building a strategic scientific agenda that is relevant at the global level but is also tailored to the needs of each region, have gathered globally over 1000 participants from 130 countries. In addition, I have been working with PREZODE's CIRAD focal point to co-construct with a more limited set of partners (~10 institutions) one of the first pilot projects of the PREZODE initiative funded by AFD in five priority countries. In collaboration with the SEGA-OI network – a regional health surveillance network led by the Commission for the Indian Ocean– the aim of the Madagascar pilot will be to develop and strengthen surveillance capacities for priority zoonotic diseases. Finally, since Madagascar is one of the recipients of PREZODE, I have been working with PREZODE's CIRAD focal point and the French Embassy in Madagascar to obtain official institutional support for the initiative at the country level via meetings with relevant Ministries.

5. Contributions to science

Preface

More than one billion people, most of them in tropical and subtropical countries, still live in extreme poverty and suffer a disproportionate burden of communicable diseases [1, 2]. Reinforcing mechanisms between human health and economic development have contributed to an overall joint trend of wealth and health in recent history, but they are also partly responsible of the great inequalities present in the world today. An important link in this relationship is the role of the environment in shaping historical and current spatial patterns of both poverty and disease [3–5]. Tropical regions have appropriate climatic and biological conditions for pathogens to develop and persist [6, 7], carrying as a result an overwhelming burden of infectious and parasitic diseases that undermine the productivity of its local populations among other economic impacts [8, 9]. In the current context of global environmental degradation, climate and land-use change, a disproportionate burden of adverse health effects is expected to be borne by tropical regions and vulnerable populations [10], which will exacerbate existing inequalities [11]. Recognition of these multiple interlinkages (Figure 1) has fostered a comprehensive multilateral commitment for human development, wellbeing and environmental preservation embodied in the Sustainable Development Goals (SDGs) [12]. As the SDGs guide policy and development assistance on all these fronts in the period 2015-2030, there is a need for frameworks of study and action that are integrative, multidisciplinary and systems-based, in order to tackle some of the most pressing issues in sustainable development today.

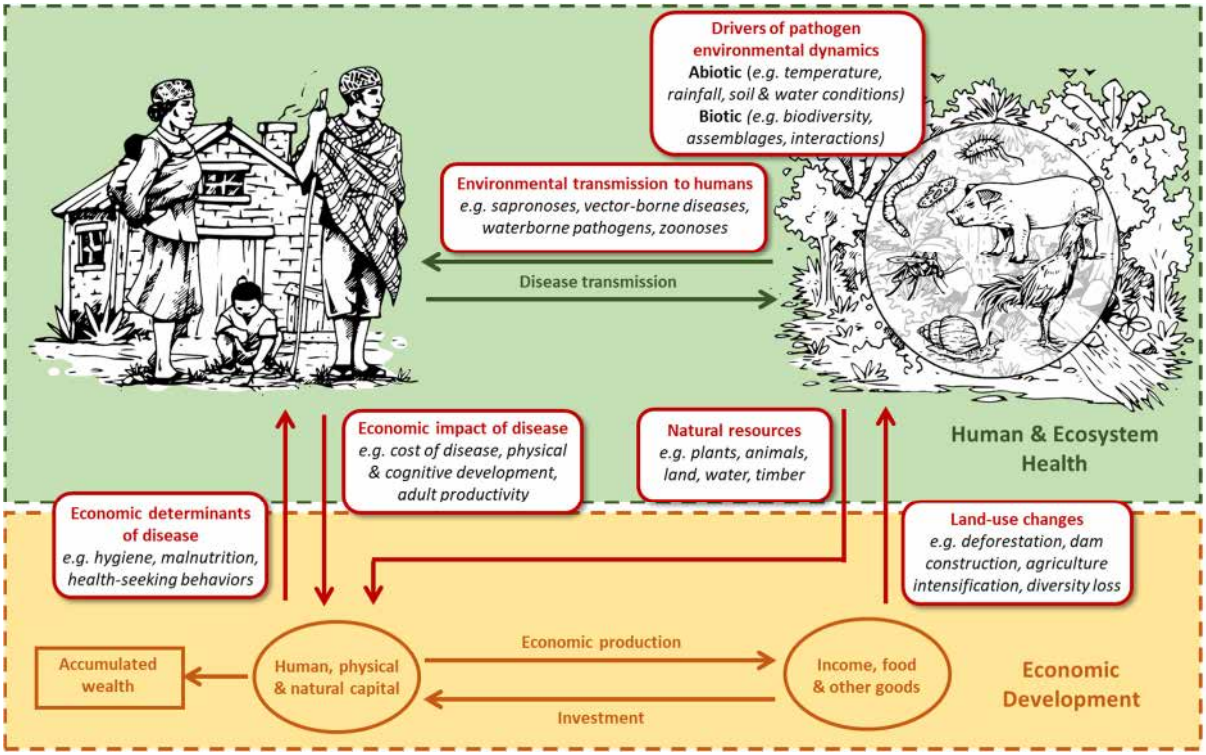

Figure 1. Coupled natural and human systems: feedbacks between ecosystems, infectious diseases and economic development. Many human pathogens in tropical regions, including those that cause NTDs, spend part of their lifecycle outside the human host, where environmental conditions drive their ecology and transmission (upper panel). Ecosystem and disease dynamics influence key forms of capital necessary for economic development of at-risk human communities (lower panel). Simultaneously, economic activities and resources affect those same dynamics by altering vulnerability to disease and introducing land-use changes [13].

My multidisciplinary background prior to becoming a researcher at the French Institute for Sustainable Development (IRD) has helped me better understand how these interactions between poverty, environmental degradation and human diseases take place in real-world settings and how solutions can be implemented to address them based on this knowledge. After finishing 5 years of training as a veterinary doctor at the University "Complutense de Madrid", I carried out a European Master in Public Health (2009-2011) during which gained experience through internships with the Guatemalan Ministry of Public Health on vector-borne disease control, and with the WHO French Cities-Health Network on social determinants of health and urban health. These biomedical skills, combined with knowledge in environmental health and social determinants of health, allowed me to develop a multidisciplinary PhD project funded by the French Doctoral Network in Public Health. My PhD, carried out in 2011-2014 under the supervision of disease ecologists Jean François Guégan and Benjamin Roche (IRD), aimed to assess the interactions between poverty, environmental factors and Buruli ulcer disease, combining extensive ecological fieldwork in Cameroon with statistical and mathematical modelling analyses. From 2015 to 2017, I held a post-doctoral fellowship in global health and social medicine at Harvard Medical School supervised by economist Matthew Bonds and epidemiologist Megan Murray. During the same period, I became Research Manager for the healthcare NGO Pivot, founded by Matthew Bonds in 2014 and based in Madagascar, where I spent most of my time. During this period I focused my research on better understanding health inequalities and conducting impact evaluations of health interventions in the context of Pivot's health systems strengthening program in Ifanadiana District, Madagascar.

This disparate set of experiences and research interests has strongly shaped my scientific agenda, approaches and contributions (Figure 2). First, methods in disease ecology and economics that I learned during my PhD and postdoc allowed me to develop research approaches to understand, from both a theoretical and empirical perspective, how simultaneously considering environmental dynamics of pathogens, economic dynamics, and human health, can help inform disease control activities *(Section 1. Integrated research approaches to improve the control of tropical diseases of poverty*). Second, my experience in Ifanadiana made me realize that, while there has been incredible progress in the modelling of infectious diseases in the academic literature, these methods are rarely used in a way that informs the implementation of control activities at the local level. I am trying to fill this gap by adapting data collection methods and analyses for a number of relevant diseases in the area so that research outputs can be used by local health actors (*Section 2. Surveillance and modelling of tropical diseases at the local level*). Third, even though understanding the ecological and socio-economic determinants of health can lead to better strategies for disease prevention and control, this should not prevent us from investing in the health systems that treat people against these diseases. Through my work with the NGO Pivot, I became aware of the potential that horizontal approaches to health care delivery such as health systems strengthening interventions and universal health coverage policies have for sustainably improving population health. My research on this front has focused on building robust data collection and evaluation methods (observational, quasi-experimental) to measure the impact of such approaches and inform their implementation (*3. Evaluation of interventions to achieve universal health coverage*). Finally, as my implementation research work has consistently revealed the persistence of geographic inequalities in Ifanadiana over time, health geography approaches have emerged as a necessary expansion of my research agenda, where I attempt to precisely characterize geographic inequalities in both potential and realized access to health care at different levels of care (*4. The geography of health care access under HSS support*). In the next few pages I summarize some of my main contributions over the past ten years to these four important global health research topics.

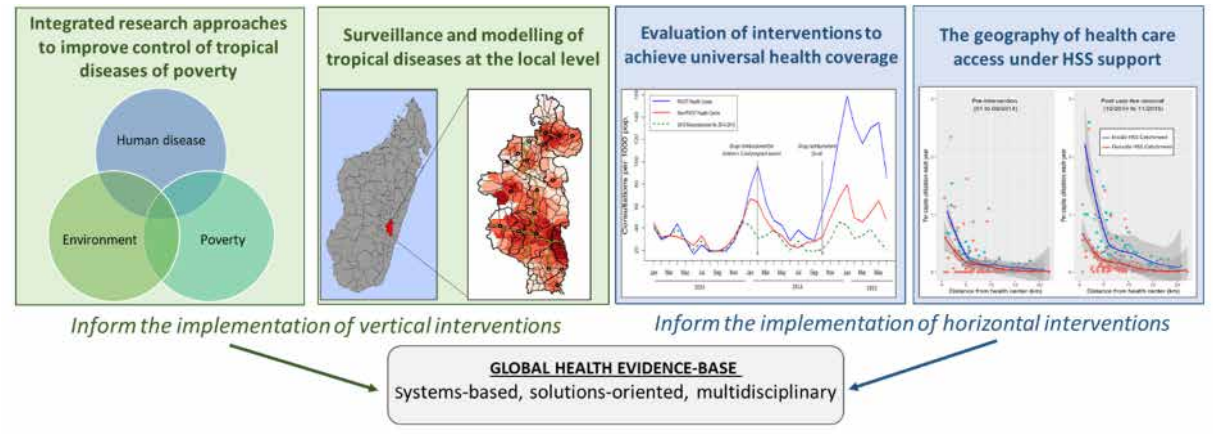

Figure 2. Main contributions of my research to the field of global health. Schematics show my four main areas of research, two of which aim to inform the implementation of vertical interventions (disease-focused) while the other two aim to inform the implementation of horizontal interventions (systems-based).

Integrated research approaches to improve the control of tropical diseases of poverty

My early research interest concerned the interactions between poverty, environmental risk factors and the emergence or persistence of infectious diseases, inspired by previous work on disease-driven poverty traps [5, 14, 15]. In this sense, Neglected Tropical Diseases (NTDs), a group of chronic, disfiguring and disabling conditions, represent a perfect study case of strong ecological and economic feedbacks with human disease. This umbrella term refers to 17 parasitic, viral, and bacterial infections highly embedded in particular tropical ecosystems and transmitted through environmental pathways [16, 17]. Land use change - by altering human behaviour, ecological interactions, habitat quality and biodiversity – can strongly affect the dynamics of these diseases and have an overwhelming impact on poor vulnerable populations. Most of the global burden of NTDs accumulates in sub-Saharan Africa where they are the most common infections of the poorest 500 million, thriving under conditions of poverty, poor sanitation and malnutrition [18, 19]. They constitute a major barrier for the economic development of the populations affected, impairing child growth, education and limiting adult productivity [17]. In addition, because they are highly debilitating conditions, co-infections are common and overlap geographically with HIV, tuberculosis and malaria [20].

Cheap available treatments exist for a large number of these conditions [21], and indeed biomedical interventions via mass administration of preventive chemotherapy are the cornerstone of the fight against many NTDs. However, the environmental persistence of many of these diseases in combination with a strong link with poverty means that a successful, sustainable decrease in the burden of many NTDs requires a broader understanding of interactions taking place in coupled human-environmental systems. My work in this area started during my PhD, where I studied these interactions in the context of a single disease, Buruli ulcer, to better understand the ecological factors leading to higher infection risk, its mode of transmission to humans, and its economic impacts in endemic areas. Then, I expanded the scope of my research during my postdoc to encompass other disease systems with the development of integrated modelling frameworks for the control of NTDs across a gradient of transmission modes, and for the study of how livestock diseases impact the rural poor.

The ecology, transmission and economic consequences of Buruli ulcer

Buruli ulcer, a devastating skin disease caused by the environmental pathogen *Mycobacterium ulcerans*, is probably the least studied of all Neglected Tropical Diseases. Discovered in the 1960s, it has rapidly emerged in tropical and subtropical countries across the globe and currently infects 5000 new people every year, most of them in rural areas of Central and Western Africa [22]. Although initial stages of the disease can be treated with an 8-week antibiotic regime (*i.e.* nodules, plaques, small ulcers), poor access to treatment in these regions frequently leads to catastrophic disease progression. Thus, one in four cases end up with functional limitations for life as a consequence of complicated stages (*i.e.* extensive ulcers, osteomyelitis) that require invasive surgical procedures and lengthy hospital stays. These pathological problems are closely tied with great socio-economic consequences [23, 24]. Early detection and treatment of cases, the main WHO strategy for Buruli ulcer control, can avert much of the unnecessary suffering borne by those affected [16]. Yet, our poor understanding of the environmental mechanisms that drive human infections greatly undermines our capacity to detect cases in a timely manner. Emergence and geographical distribution of Buruli ulcer have been consistently associated with aquatic ecosystems. Prevalence of the disease is concentrated along the basin of slow flowing rivers, with areas of low elevation and located in drainage basins generally at higher risk [25]. Land use changes due to agricultural practices, deforestation, or to the construction of dams and roads have contributed to create Buruli ulcer endemic areas [25]. However, the ecology of *M. ulcerans* and transmission of Buruli ulcer to human populations is still poorly understood, and it is unclear whether a direct entry into the skin [26] or a vector transmission through the bites of water bugs [27, 28] are contributing to the disease burden.

My PhD sought to provide insights into the ecological mechanisms allowing for *M. ulcerans* to grow, persist and be transmitted from the environment to humans, using a multidisciplinary field-based approach in Cameroon (Figure 3). For this, I characterized the ecological dynamics of *M. ulcerans* with unprecedented detail in 32 aquatic communities of two Buruli ulcer endemic regions during one year, with monthly sampling in a large variety of streams, rivers, swamps, and flooded areas. In each site, I measured the physicochemical characteristics of the water, collected all aquatic macro-invertebrates and vertebrates (over 230,000 individuals) using standardized methods, identified them taxonomically in the laboratory, and selected over 3,000 pools for qPCR analysis to detect *M. ulcerans* DNA across taxonomic groups, seasons and environments. This resulted in the creation of the largest database for the study of *M. ulcerans* ecology to date [29]. A simple exploratory analysis of this database revealed that *M. ulcerans* was present in nearly all aquatic organisms tested, with colonization dynamics that fluctuated along the year, with important differences between taxonomic groups and sites [29]. Statistical analyses of biotic and abiotic factors associated with *M. ulcerans* prevalence suggested that the bacteria thrived in periods of intensive rainfall, and optimal physico-chemical conditions in lentic ecosystems (*i.e.* low water flow, low oxygen, mildly acidic *pH*, high temperature), favouring the environmental persistence of the pathogen and colonization of aquatic hosts [30]. However, under unfavorable water conditions, *M. ulcerans* seemed to persist in the environment thanks to a trophic transmission between aquatic hosts [30].

Collaborations with other disease ecologists allowed us to further exploit this database to gain deeper insights into the ecological processes at play that determined *M. ulcerans* environmental persistence. For instance, a thorough analysis of the impact of community-level factors on *M. ulcerans* prevalence by postdoctoral researcher Gabriel Garcia Pena revealed that niche-based extinction of species increased the prevalence of the pathogen in aquatic communities, providing support to the

dilution effect in our particular context [31]. Furthermore, remote sensing and spatial analyses by PhD student Kevin Carolan explored how factors at larger spatial scales beyond the individual site's characteristics could influence *M. ulcerans* presence. We found that the land cover and topography of the watershed was associated with the occurrence of *M. ulcerans*, which could allow for predictions of *M. ulcerans* presence over larger geographical regions [32]. We used a similar approach to understand the environmental niche of water bugs, finding that the predicted niche of water bugs and the spatial distribution of Buruli ulcer were significantly correlated [33].

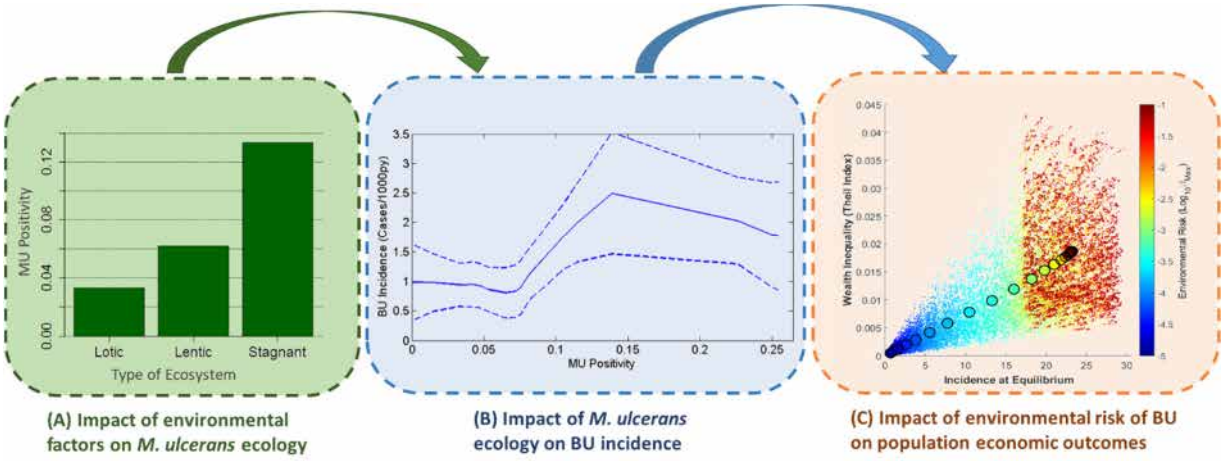

Figure 3. Understanding feedbacks between environment, Buruli ulcer and economic development. (A) Prevalence of the bacteria in aquatic sites were favoured by specific conditions in stagnant and slow-flowing (lentic) ecosystems [30]. (B) Spatial and temporal patterns of Buruli ulcer (y-axis) were influenced by the environmental prevalence of *M. ulcerans* (x-axis) [34]. (C) Increases in wealth inequalities (y-axis) as a function of BU incidence (x-axis) and *M. ulcerans* environmental load (colour gradient) [35].

Time series analyses of Buruli ulcer incidence by PhD student Jordi Landier confirmed that Buruli ulcer incidence varied seasonally in these areas similarly to *M. ulcerans* environmental prevalence, and suggested that variations in the water level and rainfall can be behind these fluctuations [36]. Thus, we associated via mathematical modelling these environmental dynamics of *M. ulcerans* with the spatial and temporal patterns of Buruli ulcer incidence in human populations in the two endemic regions to better understand their relationship and gain insights into *M. ulcerans* mode of transmission to humans. This provided the first field-based evidence that an environmental transmission to humans is likely to play a greater role than a vector transmission in endemic areas, and suggested that *M. ulcerans* environmental load could predict in advance the temporal and spatial patterns of Buruli ulcer incidence [34].

In order to understand the impact of high-risk ecosystems on the emergence of Buruli ulcer clusters and consequently on the economic development of the populations affected, we developed a coupled economic-epidemiological model that incorporated a gradient in environmental risk [35]. We used an individual-based approach to capture disparities in vulnerability to Buruli ulcer and in access to treatment as functions of economic resources in a disease model. Simultaneously, we accounted for reductions in physical capital in an economic growth model as a result of disease or permanent handicap. We showed that, for tropical diseases that are rare but highly disabling like Buruli ulcer, a combination of environmental and socio-economic feedbacks can drive important inequalities at the population level, with disproportionate impacts on the poorest socio-economic groups [35].

Integrated modelling frameworks for NTDs and livestock diseases

During my postdoctoral fellowship, I sought to continue exploring the kind of integrated modelling frameworks I had started with Buruli ulcer, but with broader applications for the control of other tropical diseases of poverty. Through a collaboration with my postdoc supervisor Matthew Bonds, Giulio de Leo (Stanford University) and other infectious disease modellers, we adapted models of disease-driven poverty traps to better understand how diseases across a different spectrum of environmental persistence could affect the success of common biomedical control strategies, and how this could impact economic dynamics at the population level [13]. We built on traditional systems in disease ecology and epidemiology [37–39], and developed a general infectious disease model that accounts for direct and environmental pathways of disease transmission. The model is meant to represent the dynamics of NTDs and other tropical diseases of poverty across a wide spectrum of transmission strategies (Figure 4), spanning from human-to-human contagious diseases (e.g. leprosy, trachoma) to parasitic worms (e.g. schistosomiasis), waterborne bacteria (e.g. Buruli ulcer), foodborne pathogens (e.g. echinococcosis), vector-borne diseases (e.g. dengue, malaria), or zoonotic and multi-host pathogens (e.g. rabies, nipah virus).

We showed that for direct and environmentally transmitted diseases with comparable basic reproduction numbers, control can be more effectively achieved for directly-transmitted diseases through periodic medical treatment. All else being equal, the same drug-focused strategies can have a reduced efficacy for diseases where the environmental reservoir plays an important role. In the latter case, more effective control can be achieved when classic treatment strategies are complemented with interventions that act on the environmental reservoir of the pathogen or reduce exposure. We then integrated this model with economic growth models to understand the potential role of environmental drivers on disease-driven poverty traps, given that economic and environmental conditions are co-determinants of NTDs, and NTDs have well-documented negative effects on economic productivity [1, 5, 40–42]. In the case of environmentally-transmitted diseases, such as most NTDs, disease-economic dynamics are highly influenced by the dynamics of the pathogen in the environment. As a result, the same strategies that could help break a disease-driven poverty trap for directly transmitted diseases, might not be sufficient for environmentally-transmitted diseases [13].

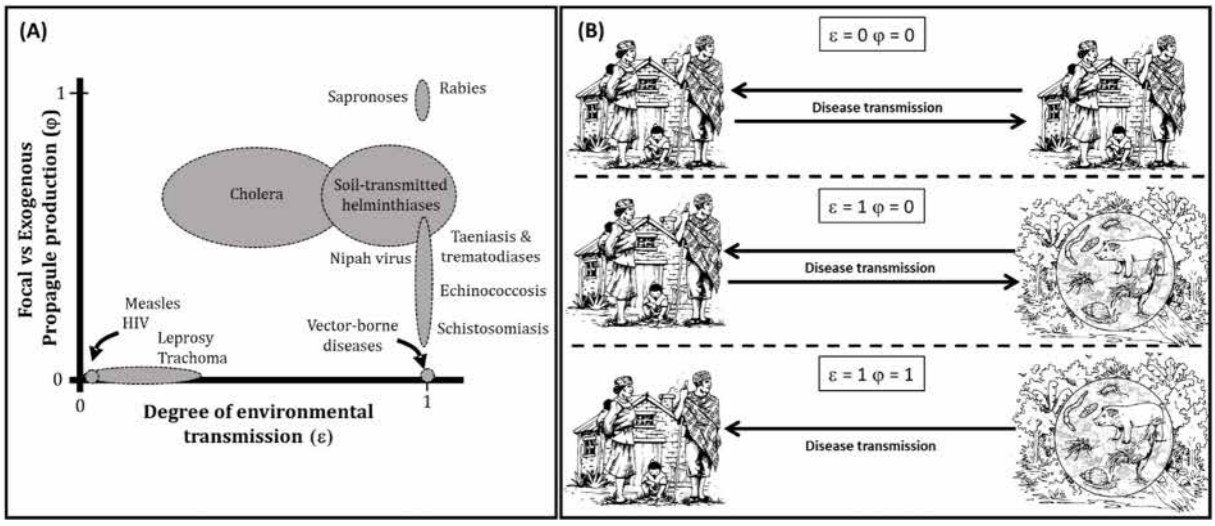

Figure 4. Conceptual framework to account for multiple pathways of disease transmission in coupled economic–epidemiological systems. (A) Classification of relevant infectious and parasitic diseases in developing countries according to two key model parameters that regulate environmental transmission. (B) Graphical representation of the three main groups of diseases according to key model parameters: directly transmitted

(top), environmentally transmitted, with focal transmission dependent on human prevalence (middle) and environmentally transmitted, driven purely by exogenous environmental factors (bottom) [13].

In addition to this work, a collaboration with veterinary researchers Cassidy Rist and Tom Gillespie (Emory University) allowed our group to adapt a similar integrated framework to study how livestock diseases can impact the health and wealth of poor rural households, both from a theoretical and empirical perspective. Indeed, livestock represent a fundamental economic and nutritional resource for many households in the developing world and a high burden of infectious diseases can limit their production potential. We developed an ecological framework for estimating the burden of poultry disease based on coupled models of infectious disease and economics [43]. The framework considers humans and livestock as co-contributors to household wellbeing, incorporating feedbacks between poultry production and human capital in disease burden estimates. We then parameterized this coupled ecological–economic model with household-level data to provide an estimate of the overall burden of poultry disease for the rural district of Ifanadiana in Madagascar, where over 72% of households rely on poultry for economic and food security [44]. Our models suggested that households may lose up to a quarter of their monthly income under existing local disease conditions, making the case for stronger support to veterinary programs that target common livestock diseases [44].

Surveillance and modelling of tropical diseases at the local level

Despite great progress in the fight against many tropical infectious diseases over the past few decades, these continue to represent a substantial morbidity and mortality burden for poor populations in developing countries [45]. Attempts to decrease infectious disease burdens in the developing world will necessarily be built around the increasing amount of data available, in combination with robust methods for estimating spatio-temporal incidence and intervention coverage rates, which can greatly inform policy and implementation. The availability of free remotely-sensed information (e.g. MODIS, SRTM, CHIRPS, Sentinel) has popularized the use of satellite remote sensing methods in health research [46]. As a result, environmental and anthropogenic factors that play a role in infectious disease transmission can be assessed through proxies to explain observed dynamics or predict future trends via precision health mapping [46, 47]. Studies typically use satellite imagery at different levels of resolution (spatial and temporal) to characterize seasonal changes in climatic factors such as rainfall, temperature, vegetation indices (e.g. EVI, NDVI) as well as spatial anthropogenic gradients in land cover [48–50]. One massive effort underway is the Malaria Atlas Project, which combines data from malaria national programs (passive surveillance) with national surveys (e.g. Malaria Indicator Surveys, Demographic and Health Surveys, and Multiple Indicator Cluster Surveys) and satellite imagery for sub-Saharan Africa. Among other applications, this approach has allowed generating accurate spatial estimates of malaria mortality rates for the whole region [51], developing decision support tools for strategic planning by malaria control programmes [52], and obtaining robust estimations of malaria treatment coverage through multi-country studies [53]. Results from these and similar studies on multiple other disease systems are allowing multilateral organizations, donors and national governments to prioritize efforts and investments based on solid information.

However, there is a substantial gap between our collective analytic capabilities and the use of those capabilities to solve problems where they matter the most – in areas of extreme poverty with high burdens of disease. For precision health mapping and similar approaches to lead to actionable interventions, the global relationships between disease and its socio-ecological risk factors must remain at the fine spatial resolutions relevant to public health actors that implement control activities.

A key unit of implementation in most developing countries, both for Ministries of Health and the NGOs supporting them, is the health district. Providing district health officers and their partners with estimates of disease incidence or risk at the scale of the villages within their districts could allow them to tailor disease control activities to the spatio-temporal distribution of local disease burdens. My work since 2015 with the healthcare NGO Pivot in Ifanadiana District (Madagascar), initially as its Research Manager and now as its Associate Scientific Director, has driven me to attempt adapting these methods, which are common in disease ecology research, but in a way that can be useful to health actors working at local scales. My research on this topic includes i) assessing whether associations seen in precision health mapping at national or multi-country scales hold true at finer resolutions, with a first study on diarrheal illness, ii) improving the precision and spatial resolution of routine disease surveillance data, with a focus on malaria, and iii) evaluating the impact of elimination programs using complementary information to standard evaluation methods, through the case of lymphatic filariasis.

Precision health mapping of diarrheal disease

Many diseases can be the object of precision health mapping exercises at the local level. We chose to begin our efforts in Ifanadiana with diarrheal disease because the determinants of environmental suitability for diarrheal pathogens, such as climate [54, 55] and land cover [56], are well known. Moreover, hydrological networks and WASH (water, sanitation, and hygiene) infrastructure can influence transmission dynamics and individual risk [56, 57]. It can also be a good target of environmental interventions to decrease disease burdens, since upstream land cover has been recently shown in multi-country studies to predict diarrheal disease prevalence in rural areas of the tropics [56], with cumulative effects for populations that are downstream of sources of water contamination (e.g. livestock or agricultural run-off) [58]. The conditions in Ifanadiana were ideal to test these relationships: the district comprises a protected tropical rainforest, large areas of agricultural land, a steep east–west elevation gradient, and high exposure to diarrheal pathogens due to widespread poverty and poor WASH infrastructure.

Working with Michelle Evans, PhD candidate at the University of Georgia Athens (John Drake's lab) during a PhD internship that I supervised at Pivot in Ifanadiana, we interrogated whether these large-scale associations held true in our district to help inform program implementation. For this, we used multiple spatio-temporal datasets of childhood diarrheal disease in Ifanadiana district collected at the village and commune level over 5 years, which included a district-representative longitudinal cohort (with surveys equivalent to those used in multi-country studies) and monthly reports on diarrheal incidence from all its health centers (Figure 5). We used statistical models to identify consistent socio-ecological risk factors of diarrheal disease, finding that environmental factors, which most precision mapping studies heavily rely on due to the wide availability of remotely sensed data, helped explain temporal but not spatial patterns of disease [59]. In our study area, only socio-economic variables, which have weak spatial signatures, were important predictors of spatial patterns of disease. Our models performed poorly overall, which limits their operational use for the Ministry of Health, Pivot, or other health actors.

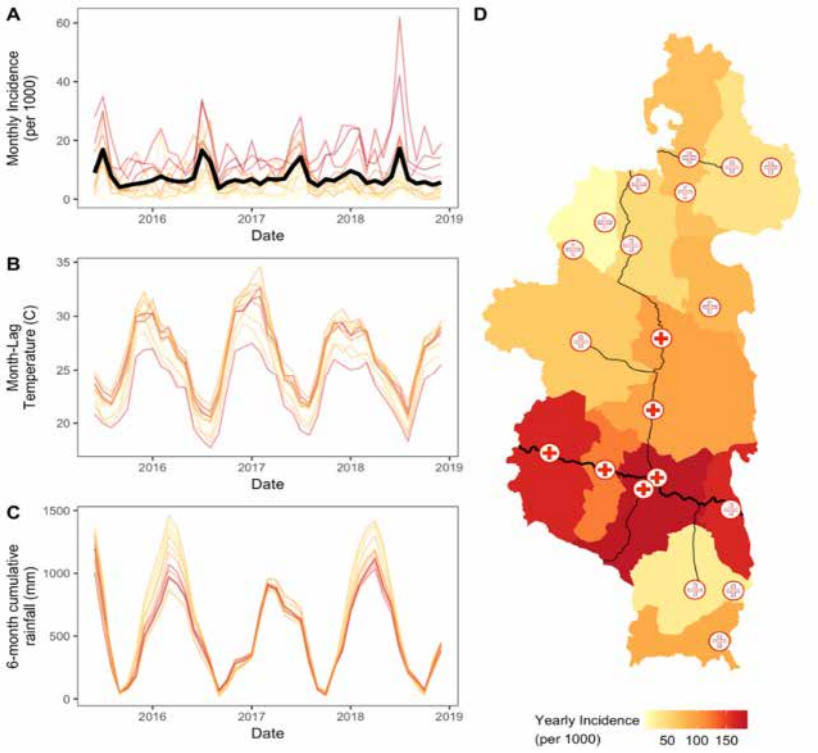

Figure 5. Commune-level diarrhoeal incidence in children under five across time and space. (A) Monthly diarrhoeal disease incidence for each commune, with the mean incidence across all communes plotted in the bold black line. (B) One-month lagged temperature values for each commune. (C) Three-month cumulative rainfall values for each commune. (D) Map of yearly incidence by commune for 2017. Health centres supported by Pivot are red-filled symbols as in figure 2Line colours in (A), (B) and (C) correspond to incidence values in (D) [59].

At a time where 'big data' solutions are increasingly used to optimize local public health interventions, our findings highlighted the limitations of precision health mapping approaches at local scales, challenging the conventional wisdom that associations found at broad scales can simply be downscaled to inform local implementation. Despite these results, we are working on precision health mapping and modelling of other disease systems in Ifanadiana, such as malaria, to see if the higher incidence, better reporting, and (probably) stronger environmental signatures allow us to predict more reliably disease dynamics. However, this requires improvements in the precision and spatial resolution of routine surveillance data (next section).

Malaria surveillance at local scales

Reliable surveillance systems are essential for identifying disease outbreaks and allocating resources to ensure universal access to diagnostics and treatment for endemic diseases. Yet, most countries with high disease burdens such as Madagascar still rely on passive surveillance alone, which is known to miss the vast majority of cases in rural settings due to persistently low access to health care[60–63]. This is especially true for remote populations in rural areas, as health centers are sparsely distributed and health care utilization tends to decrease exponentially with increasing distance to a health facility [64–68]. Though passive surveillance is helpful at the national level to identify districts with higher transmission and track stock needs for a variety of diseases, innovations are urgently needed to allow these data to inform local implementation of control interventions. In particular, improving the quality of malaria surveillance is critical under the WHO Global Technical Strategy for Malaria 2016–2030 in order to reach the goal of a 90% reduction in malaria mortality [69]. All of the above issues are present in the rural district of Ifanadiana, where malaria transmission is among the highest in Madagascar and represents about one third of all primary care consultations every year. In order to help Pivot and the Ministry of Health better understand local malaria transmission, we needed to develop a method to obtain accurate estimates of spatio-temporal incidence at the level of villages within the district, in a way that limits biases in routine surveillance data due to low access to care.

I started exploring this work with Elizabeth Hyde, medical student at Stanford University and recipient of a "Med Scholar Research Program" award to do research with Pivot in Ifanadiana for one year, which I supervised. For this, we used a geographically-explicit patient dataset of nearly 300,000 consultations and 75,000 malaria cases diagnosed at the District's health centers over four years. We adjusted malaria incidence at the village level using a benchmark multiplier method combined with a healthcare utilization index, which we obtained following a precise spatio-temporal model of local determinants of health care access. Using multiple criteria for cross-validation, including comparisons with a district-representative longitudinal cohort, we show that our estimates are less sensitive to the distance decay observed in geographic access to care or to sudden changes in financial access due to user-fee exemption programs in place [70]. Importantly, we showed that passive surveillance missed about 4 in every 5 cases of malaria, and failed to detect spatial clusters of high malaria transmission clusters in the district (Figure 6). Although data collection was particularly time-consuming because we had to manually enter patient information electronically from health centers' paper registries, we believe our methods could be easily scaled-up in the near future thanks to the increasing availability of e-health platforms for disease surveillance in Madagascar and across the developing world. Thanks to funding from the French National Research Agency, we are currently working on further improving these methods (see future research), using the resulting adjusted data to conduct statistical and mathematical models of local malaria transmission that will help us predict trends in e-health dashboards and simulate the potential impact of field interventions to reduce transmission in the district prior to their implementation.

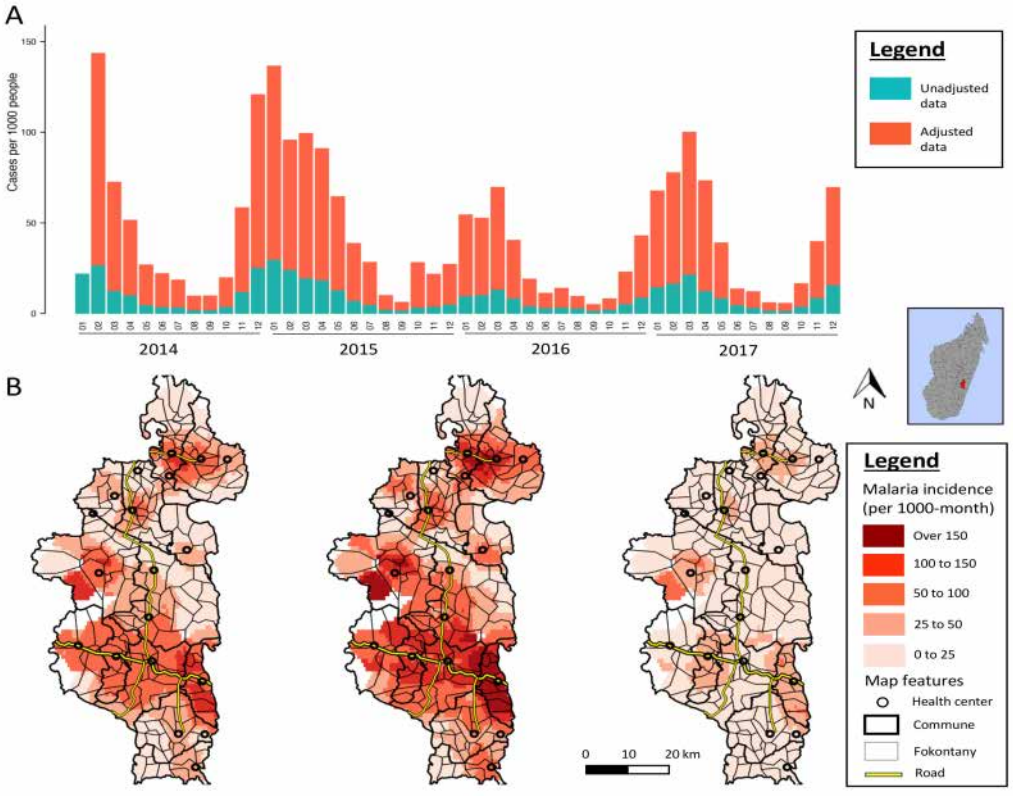

Figure 6. Temporal and spatial dynamics of adjusted monthly malaria incidence in Ifanadiana, 2014–2017. (A) Average number of new cases per 1000 population of all ages per month in the most plausible adjusted dataset (orange) and before adjustment (teal). (B) Geographic distribution of malaria, averaged over all months (left), high season months (December to May; center), and low season months (June to November; right). Color gradient represents average monthly malaria incidence per 1000 population [70].

Local assessments of lymphatic filariasis elimination

Related to empirical work conducted in Ifanadiana for improving local control of tropical diseases, I have continued to pursue my interest on NTDs, in this case via the study of lymphatic filariasis elimination programs. This disease with chronic disabling consequences is targeted for global elimination via annual rounds of mass drug administration (MDA) carried out by National Programmes in endemic countries [71]. Transmission assessment surveys (TAS) in school-attending children are the WHO-recommended tool helping National Programmes decide where MDA can be stopped [72], but the validity of their conclusions has rarely been assessed. In Madagascar, the National Programme has made substantial progress in reducing lymphatic filariasis transmission, with a priority for high prevalence districts such as Ifanadiana [73]. However, since the Programme was launched in 2004, no study had evaluated its impact on transmission, contributing to a dire lack of literature on lymphatic filariasis in Madagascar. Working with the head of the National Programme, Holivololona Rabenantoandro and Malagasy MPH student Estelle M. Raza-Fanomezanjanahary, we carried out the first school-based TAS in the island, in addition to two concurrent community surveys in children and adults (~6,000 individuals), to assess transmission of lymphatic filariasis in four health districts of south-eastern Madagascar (Figure 7). This multiplicity of surveys allowed us to show that, although three of these districts were eligible to interrupting MDA based on TAS results, prevalence in adults remained remarkably high even after ten years of MDA [74]. Our KAP surveys and insights about the implementation of the National Programme, suggested that differentiated strategies and adherence for school-enrolled children and adults could be behind this contradicting results. Therefore, in addition to showing for the first time the progress of Madagascar against lymphatic filariasis, our results had broader implications for how to interpret TAS evaluations in countries where an integrated package of NTD interventions recommended by WHO is being implemented at schools, the target population of TAS evaluations. Based on these results, I obtained funding from the ARTS program at IRD for a Malagasy PhD student to model lymphatic filariasis elimination efforts and other disease control strategies in south-eastern Madagascar, co-supervised by Benjamin Roche and me.

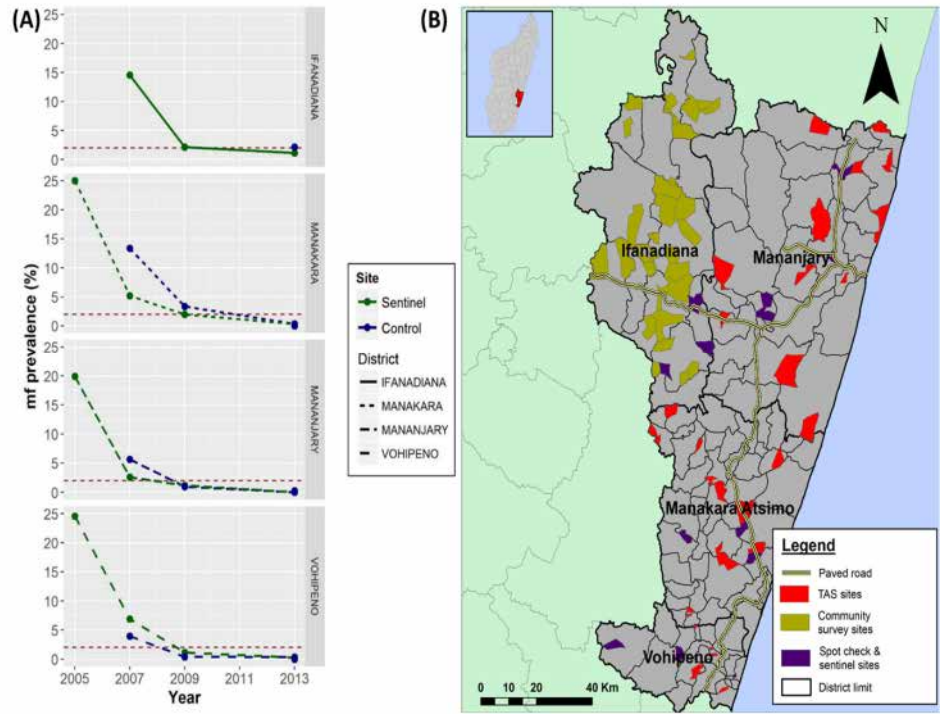

Figure 7. Assessment of lymphatic filariasis elimination in south-eastern Madagascar. (A) Trends in microfilaria prevalence over time, 2005-2013, as a result of MDA programs. (B) Three type of surveys conducted simultaneously in 2016 to assess elimination status in the area [74].

Evaluation of interventions to achieve universal health coverage

My background in disease ecology and experience working alongside NGOs and Ministries of Health in developing countries has allowed me to contribute to the understanding of particular tropical diseases such as Buruli ulcer, malaria, or lymphatic filariasis, with a goal of helping disease control efforts as described earlier, which are typically channelled through an array of vertical programs (i.e., disease-specific). The increase in support to vertical programs during the Millennium Development Goals (MDGs, 2000-2015) has had great benefits for populations in the developing world, resulting in a great expansion in the coverage of vaccines, bed-nets, and treatments for many infectious and parasitic diseases, and contributing to some of the greatest declines in mortality and morbidity for those in poverty [21, 75]. However, without parallel investments in stronger health systems, this focus on vertical programs can have in certain contexts negative spill over effects on health systems, such as service fragmentation, reduced effectiveness and increased barriers to health care access in non-targeted populations [76]. The UN post-MDGs agenda, articulated through the SDGs reflected an attempt to address this by explicitly focusing on sector-wide approaches such as health systems strengthening (HSS) and universal health coverage (UHC). The WHO has estimated that in order to achieve the health-related SDGs, nearly three quarters of all additional required investments for low- and middle-income countries in the 2015-2030 period should be allocated to HSS, UHC, and other sector wide approaches (Figure 8), amounting to about 300 billion per year by 2030 [77]. Such a radical shift in priorities requires a profound rethinking of the evidence necessary and appropriate evaluation methodologies to inform funding allocation and implementation, because the current evidence base to inform such horizontal integration is woefully inadequate [76, 78, 79].

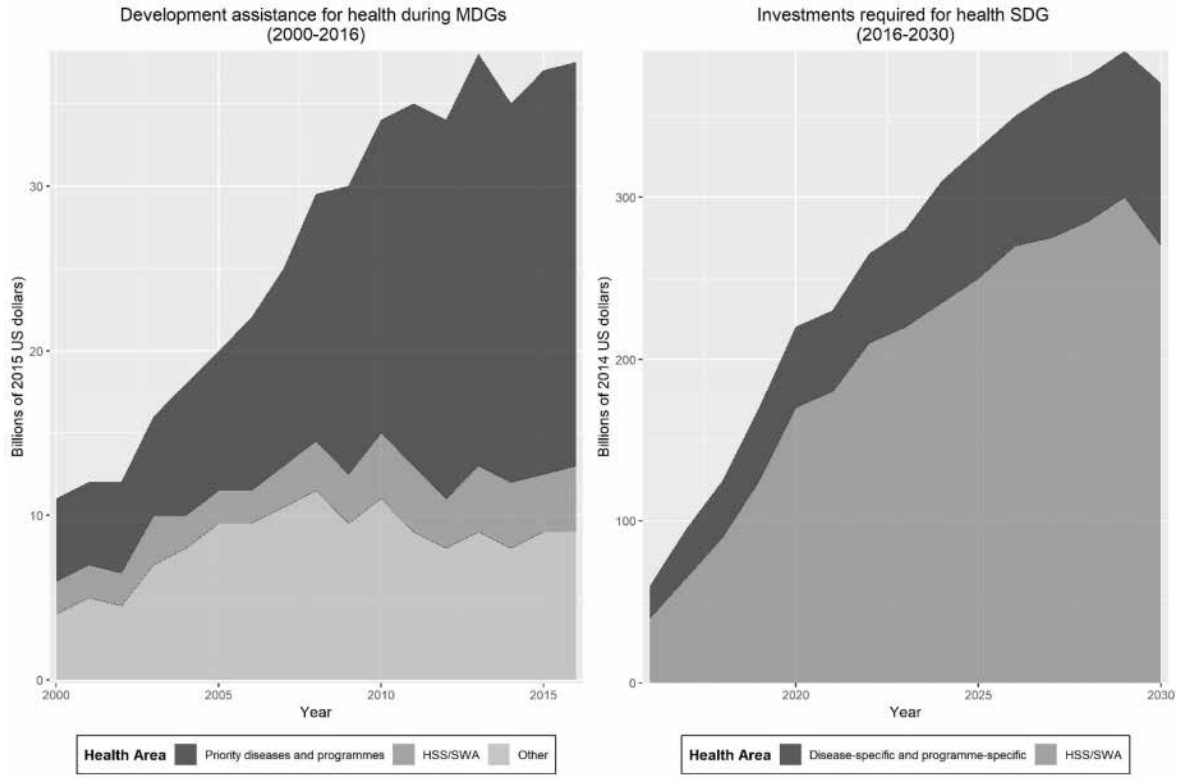

Figure 8. Shift in investments for health, from the Millennium Development Goals (2000-2015) to the Sustainable Development Goals period (2016-2030) [80]**.** Left panel shows total development assistance for health per year, adapted from the Institute for Health Metrics and Evaluation (2016). Right panel shows projected additional investments required in 67 low-income and middle-income countries to meet the health-related SDG3, adapted from Stemberg *et al.* (2017).

One of the most important questions in global health is why known technologies – those that are proven to work in certain settings – systematically fail to reach the people for whom they are intended. Half of the world's population lacks access to essential health services [81], and the majority of child deaths in sub-Saharan Africa are due to illnesses – diarrhoea, malaria, pneumonia – for which solutions are known, cheap and effective if they reach patients in need. For example, oral rehydration therapy can reduce 90% of diarrhoea-related child deaths globally, but only 4 in 10 children receive the treatment [82]. In the majority of developing countries, Ministries of Health have set national policies based on international standards, but how best to implement those policies even at small scales remains largely unknown. The challenge is that even simple technologies require complex delivery systems - trained health workers, infrastructure, supplies, and medicines - to align at the point of care. Breakdowns occur at different scales – from individual community health workers to health care facilities or national supply chains – and are self-reinforcing [83].

Randomized controlled trials are often perceived as the gold standard methodology for impact evaluation in global health and, more broadly, in international development. Since the year 2000 hundreds of RCTs have generated a vast amount of evidence and informed international guidelines, for key areas of global health [79, 84–86], but these have focused on evaluating discrete biomedical interventions for either the prevention, diagnosis or treatment of a particular disease[84, 87], largely implemented via vertical programs. In contrast, sector-wide approaches, with cross-cutting benefits but intrinsically more complex, are less amenable to RCT evaluation [88, 89], and therefore have generated less "high-quality evidence" for their wider adoption. In this sense, a big focus of my research over the past few years, starting during my postdoc and continuing as a researcher at IRD, has been to build robust data collection and evaluation methods (observational, quasi-experimental) in parallel a HSS-UHC intervention implemented in Ifanadiana District. Our collaboration is producing some of the most rigorous evidence on the impact of HSS on population health and the benefits and limits of standard UHC policies for local populations. In addition to allowing for rigorous research to be done at lower cost, the use of quasi-experimental observational methods enables health actors to keep control of the implementation process and the beneficiary population, unlike in most RCTs [80].

Impact of HSS on healthcare coverage, inequalities and mortality

UHC policies are based on a shared vision that primary health care and health services be "high quality, safe, comprehensive, integrated, accessible, available, and affordable for everyone everywhere" [90]. Achieving UHC requires health system strengthening (HSS) to ensure the reliable availability of quality health care. Madagascar is currently piloting a national UHC policy in one of the least funded health systems in the world, and one such pilots is in Ifanadiana District. The choice of Ifanadiana is not random: a partnership between the Ministry of Public Health (MoPH) and Pivot is strengthening the district health system at all levels of care: hospital, health centers, and a network of community health workers. This intervention is structured through the integration of clinical programs, health system "readiness" and information systems. The clinical programs include child health, with a focus on malnutrition and integrated management of child illness (IMCI); maternal and reproductive health; social support; and infectious disease programs, with a focus on tuberculosis, malaria and emerging diseases. Readiness includes infrastructure and sanitation, staffing and equipment to improve the quality of care; procurement systems; an ambulance network; trainings, frequent supervision and coaching of health staff. As part of the vision for UHC to increase health care access and reduce financial vulnerability, user fees are removed at all levels of care and social support is provided to vulnerable patients. The core activities in the first years covered approximately one third

of the district, which allowed us to compare the evolution in areas supported by the intervention and in the rest of the district.

To evaluate changes in health system coverage and mortality rates, we are using a comprehensive data system that combines a district-representative longitudinal cohort (the "Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation" or "IHOPE" for short) of 1600 households conducted every 2-years [91], together with consultation data from all healthcare facilities. We pay particular attention to the evolution of economic and geographic inequalities, and to the use of all these results for improving program implementation over time. Early on in the HSS intervention, we determined via baseline surveys that conditions in Ifanadiana District were quite dramatic, with child and maternal mortality rates that doubled average rates for Madagascar and about three quarters of the population living in extreme poverty [92]. Furthermore, we showed that low access to healthcare at baseline was associated with both financial and geographic barriers, and that user-fee exemptions implemented in 2014 had immediate and strong impacts on healthcare utilization at the primary care level [93]. Results from subsequent waves of the cohort revealed substantial improvements in care seeking and economic inequalities, both central goals of UHC policies [94, 95]. Coverage from 2014 to 2018 increased by more than 4% per year for care seeking in children and adults, and for facility birth deliveries (Figure 9), even in the poorest economic groups. Despite improvements in the intervention area in all coverage and mortality indicators assessed, differences with the rest of the district for maternal care coverage and under 5 mortality rates were modest [94, 95]. This could be associated with persistent geographic inequalities in access to care observed in the intervention area during the study period. Our results provide compelling evidence of the population-level effects of HSS interventions, but also warn about the gaps in care that can persist unless public health systems adequately strengthen community health programs in remote areas. The cohort is ongoing, and we will continue to produce evidence as the HSS-UHC intervention adapts and expands.

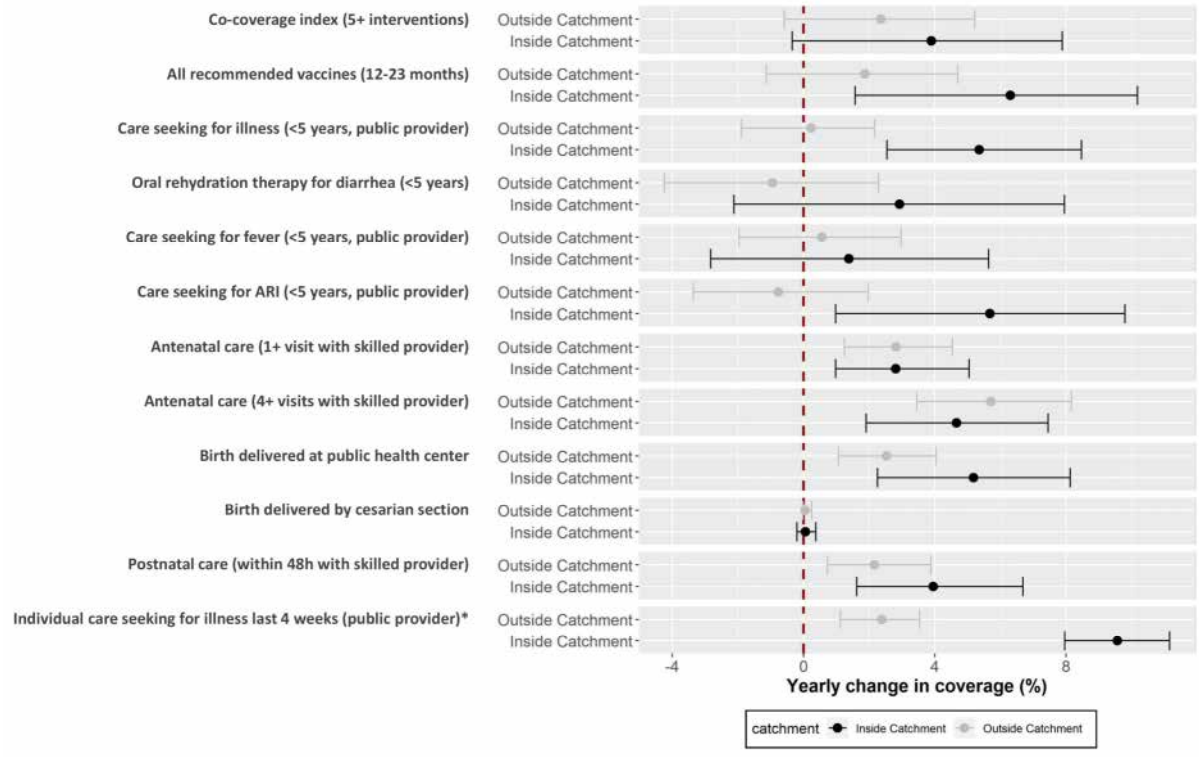

Figure 9. Annual change in key coverage indicators in Ifanadiana district, 2014 to 2018. Dots represent average model predictions for each area; whiskers represent 95% CIs based on bootstrap simulations of the model [95].

Impact of HSS on quality of care and prevention strategies

Although increases in healthcare utilization and coverage are essential, they are not necessarily sufficient for achieving substantial improvements in population health. Approximately one third of the 15.6 million avertable deaths that occurred in low and middle-income countries in 2016 were attributed to receipt of low-quality care, exceeding those attributed to non-utilization of healthcare services [96]. Ensuring the delivery of high-quality care is thus vital to attaining the health-related SDGs [97], and an international push is underway to incorporate measures of care quality when assessing the evolution of health systems in the developing world [98]. Given the large number of contributors to high-quality health systems, establishing standard indicators to measure care quality has proven challenging [98, 99]. The use of content of care (individuals' reports of what happens in a consultation) has emerged as an approach that is quantifiable, objective, and applicable to a variety of diseases and conditions [100, 101], but HSS evaluations rarely go beyond assessing healthcare access. Working with MPH student Camille Ezran, which I supervised for her M2 thesis at Stanford University, we examined changes in the content of child and maternal care over the first two years (2014-2016) of the HSS-UHC intervention in Ifanadiana, as a proxy for evaluating healthcare quality. Using information from surveys in the IHOPE cohort as well as "Service Availability and Readiness Assessments (SARA)" surveys at health facilities, we found that the intervention resulted in a general increase in the delivery of WHO-recommended healthcare outputs such as medication prescriptions, diagnostic tests, and counselling [102]. We also identified specific gaps in the quality of services delivered, where changes in healthcare outputs did not match the increases in care access observed. Besides drawing lessons for UHC in Madagascar, our study contributed to fill an urgent gap in the way HSS interventions are evaluated.

Another key determinant of population health, besides the coverage and quality of curative interventions, is the delivery of preventive interventions such as childhood immunizations. The strategies for delivering vaccines have been the same around the world for decades: by healthcare professionals, either at health facilities or through outreach activities in the form of vaccination campaigns. However, while vaccination campaigns typically receive attention as a way to rapidly improve vaccination coverage in particular populations, it is unclear how best to improve routine immunizations. On this front, I worked with Elinambinina Rajaonarifara, a Malagasy PhD student I co-supervise with Benjamin Roche (UMR MIVEGEC), to evaluate how strengthening local health systems can help improve key indicators of vaccination coverage via its impacts on routine and outreach immunizations. Using datasets at both the health system and population levels in Ifanadiana, we showed that the HSS intervention led to an increase in routine immunizations, resulting in higher vaccination coverage, a reduction in economic inequalities, and a higher proportion of timely vaccinations [103]. This was despite the fact that the intervention did not target specifically vaccine improvements themselves. The gains observed disproportionately benefited those who could most easily access services, leading to a persistence of inequalities in geographic coverage in the area that prevented achieving international coverage targets for many population groups (Figure 10). Therefore, we show that strengthening local health systems can help improve vaccination coverage but explicit efforts are necessary to vaccinate those in remote areas so that immunization goals can be reached.

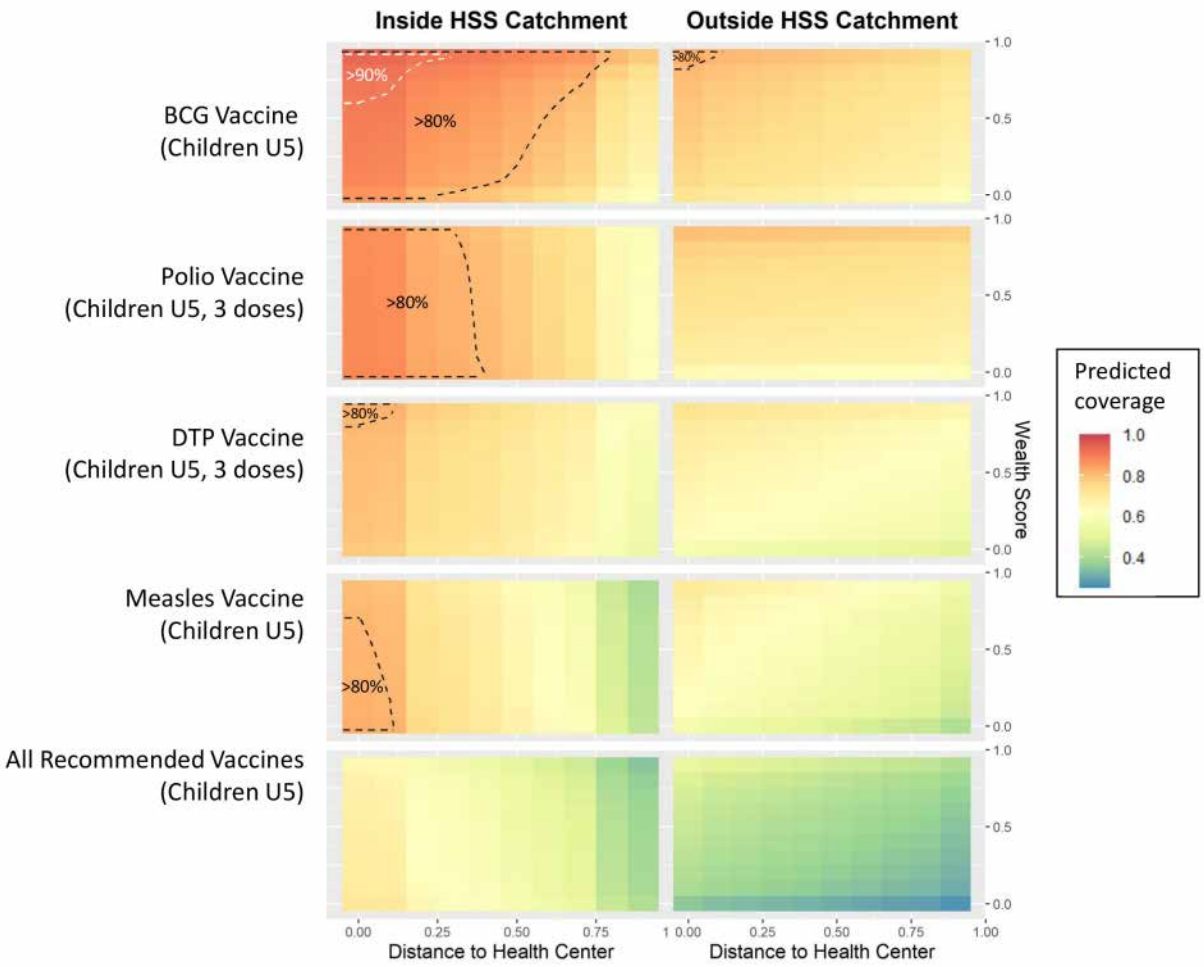

Figure 10. Predictions for achieving vaccination coverage targets for different population groups in Ifanadiana district. Graphs show in-sample predictions of vaccination coverage for the year 2018 in each intervention area, estimated from models fitted with the IHOPE cohort data 2014-2018 [103].

The geography of health care access under HSS support

A common theme across most of my early research in Ifanadiana has been the persistence of geographic inequalities in health care access despite interventions put in place to improve financial access and the quality of care. Indeed, poor geographic access to healthcare can be a great barrier towards the realization of UHC, which is supposed to make health services accessible and affordable "for everyone, everywhere". In practice, UHC policies tend to focus on financial coverage, such as through health insurance, which reduce point-of-service payments known to be barriers to care [104–108]. However, there is growing recognition that among the greatest challenges to accessing health care in rural areas of the developing world are geographic barriers: terrain, waterways, and other factors associated with physical distance between the patient and the service [64–68]. The use of primary care decreases exponentially for populations living at increasing distance of health services, which is known as the "distance decay" effect [64–68]. Distance decay in health access is equivalent to the effect of user fees [109], which can be more directly reduced or eliminated [104–108].

There are many potential solutions to improve geographic access to different levels of care. At the primary care level, these can include building new health facilities (optimizing their location according to geographic access) or supporting community health programs. Community health programs have been a cornerstone of integrated primary care efforts in recent decades [110]. For

instance, the scale-up in sub-Saharan Africa of integrated community case management (iCCM) of childhood illnesses has increased access to life-saving interventions, such as malaria care, for children under 5 years [111]. At the secondary care level, solutions also include building new hospitals in optimal locations, or the establishment of ambulance referral networks to transport patients from lower to higher levels of care. Decisions around which of these solutions to implement and how to do it necessarily depend on the context, but they all require a detailed understanding of local geographic barriers to healthcare access at each level of care. In a context where HSS efforts are in place and aim to improve access to healthcare for everyone as part of the Madagascar UHC pilots, my research in Ifanadiana has thus focused on i) developing methods that allow us to understand geographic access to care with enough precision to be informative to local health actors, and ii) evaluating potential or current strategies to reduce barriers to care in the population, and how they affect geographic access.

Improving estimates of geographic access to care for operational use

Current modelling methods of geographic access to healthcare are limited by the lack of basic geographic information (e.g. footpaths, residential areas) in rural areas of the developing world. To address this, researchers typically include available geographic information into “friction surface” algorithms that account for terrain characteristics and road networks [112–115]. These methods are the basis of the freely available tool “AccessMod” developed by WHO to support the adoption of geographic accessibility analyses into health planning [116, 117]. Moreover, their simplicity means that they are the preferred methods in multi-country studies, and the findings of such studies become a reference point for estimates of geographic access to primary and secondary care at a continental [118, 119] or global scale [120]. However, methods that rely on friction surfaces represent only a “best guess” of the routes people use in areas with poor road infrastructure and of the speed at which people travel. Their lack of precision prevents their widespread use at the local level by program managers and health workers, and could have larger implications for the validity of multi-country estimates.

Working with Malagasy postdoctoral researcher Felana Ihantamalala, we developed new methods to obtain very precise, context-specific estimates of geographic accessibility to care in Ifanadiana to help Pivot and the Ministry of Health with the design and implementation of interventions that improve access for remote populations [121]. We used a participatory approach on OpenStreetMap to map over 20,000 km of footpaths and 100,000 buildings to accurately measure distance to health facilities and community health sites for every single household in the district via the Open-Source Routing Machine (ORSM) tool (Figure 11). We obtained corresponding travel time estimates, parametrized with hundreds of hours of fieldwork and remote sensing data analyses, and we integrated all the results into a practical e-health platform for use by local health actors. We showed that the proportion of the population in Ifanadiana with poor geographic access to health facilities is much larger than typically reported elsewhere: 15% within 1h walk in Ifanadiana vs. 66% estimated for Madagascar [120]. In addition, we provided the first evidence showing gaps in the geographic coverage of community health workers [121], which are meant to be the solution to geographic barriers to care.

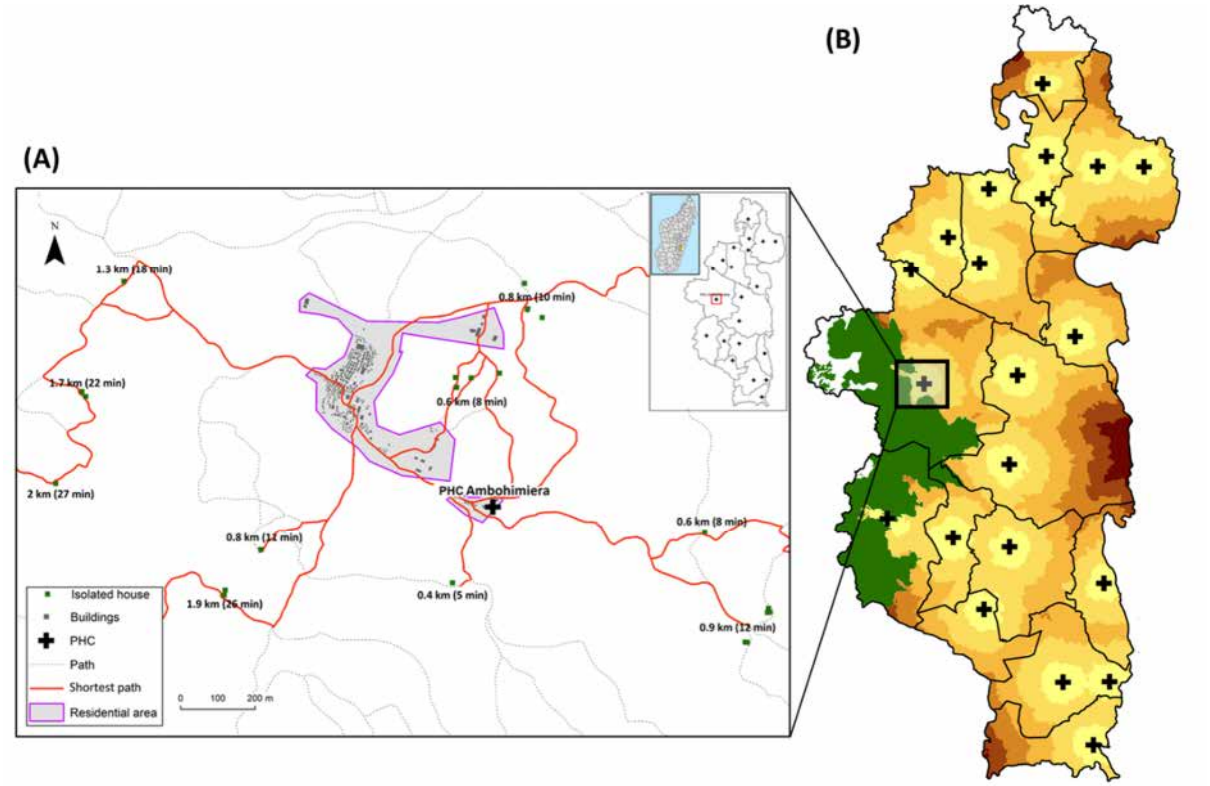

Figure 11. Estimation of distance and travel time from households to health facilities. (A) Shows an illustrative example of shortest paths obtained thought OSRM, with building values for travel distance and time to reach one of the district's PHC. (B) Shows the resulting maps of travel time for all households in Ifanadiana district, which vary from less than 1h (yellow) to over 5h (brown) [121].

Using a similar approach, we gathered information from 70 000 km of motorized trips by NGO vehicles (cars, motorcycles) in Ifanadiana District at different times of the year, and we calibrated models of motorized travel time under different terrain and climatic characteristics. We combined these estimates with the previous dataset on travel time to health facilities to obtain estimates of referral time (from facilities to hospital, by motorized vehicle) and pre-hospital time (adding to each referral the trip by foot from each household in the district to the nearest health facility), both based on shortest route algorithms and predictions from these statistical models of local travel speed [122]. We showed that about 10% of the population lived less than two hours from the hospital, and more than half lived over four hours away, with variable access depending on climatic conditions. Only the four health centers located near the paved road had referral times to the hospital within one hour. If these local results are representative of larger trends for sub-Saharan Africa, it suggests that results from multi-country studies should be taken with caution. For example, a recent continental study suggested that all regions in Madagascar had over 80% of their population living within 2 hours of a hospital [123], which is in stark contrast with the results we obtained here for Ifanadiana. This could have major implications for international health policies attempting to reach the recommended goal of ensuring that 80% of the population can access a hospital within 2 hours [124], since this threshold may be harder to reach than previously anticipated.

Impact of geographic barriers to care in a context of strengthened health systems

While the effect of geographic barriers to health care access has been abundantly studied, and the "distance decay" in health care access has been consistently characterized in multiple settings [64–68], there is little evidence on how health system change can impact the geography of health access, leaving policies that are meant to ensure access for all to be surprisingly blind to their effects on remote populations. As mentioned earlier, most countries in the world have committed to UHC through policies focused on a combination of reducing user fees at health facilities (e.g. via fee exemptions or national insurance), and expanding community health programs to serve remote populations. Whether these leading global policies designed to improve health care coverage can overcome key barriers to health care access remains unclear.

To address this important global health question, but also to inform locally the strategy of the HSS-UHC intervention in Ifanadiana district, we collected geographic residences of nearly 300,000 patients seen at all the primary healthcare facilities in the district between 2014 and 2017 to evaluate spatio-temporal changes in consultation rates at the fokontany level (smallest administrative level) following the HSS-UHC intervention. We combined this information with the precise estimates of geographic access to care described earlier, to analyze linear and non-linear relationships with distance and time to seek treatment at health facilities, as well as the impact of two programmes designed to reduce financial barriers (i.e. user-fee exemption) and geographic barriers (i.e. community programme) [125]. Our results show that despite an overall tripling in utilization rates in the study period, utilization declined dramatically within the first 5km even after the system was strengthened at the facility level and user fees had been removed (Figure 12). We observed a shift by 5km in consultation rates following user-fee removal, whereby rates in the intervention area were comparable to rates in populations living 5km closer to a facility in the rest of the district. Predictions from our statistical models provided strong evidence that UHC policies focused only on access to health facilities in our context were inadequate, leading to utilization rates of 1 consultation per capita-year or more only for about 25% of the population. However, combined with strengthened community health programs these policies can have substantial impacts on the geographic reach of the health system, as CHW care in our context ensured that children under 5 years old reached at least 2 primary care consultations per year regardless of their distance to health centers. These results provided some of the best evidence to date of the substantial gaps in care that will persist until public health systems adequately integrate professional community health programs with an expanded scope of service [125].

In addition to our research at the primary care level, the provision of emergency and hospital care has become an integral part of the global vision for UHC [126] and is a key component of the HSS-UHC intervention in Ifanadiana. Building on methods described earlier that accurately estimate referral and pre-hospital time, we studied how the local geography can limit the impact of a strengthened referral program implemented in the district, in terms of referral numbers completed [122]. We used this information to predict how strategies aimed at reducing referral time for underserved populations could improve referral numbers for remote health facilities. We showed that in our context, referral time remained the main barrier limiting the number of referrals despite HSS efforts, with an exponential decline in referrals with increasing referral time from the health facility to the hospital. The addition of two new referral centers in the north and south of the district, a strategy that the MoPH-Pivot partnership is considering for Ifanadiana, was estimated to triple the population living within two hours from a center with better emergency care capacity and nearly double the number of expected referrals. Together, our studies demonstrated how HSS-UHC interventions can be optimized for

geographic accessibility at local scales through improving the precision of travel time estimates and pairing them with data on health facility use.

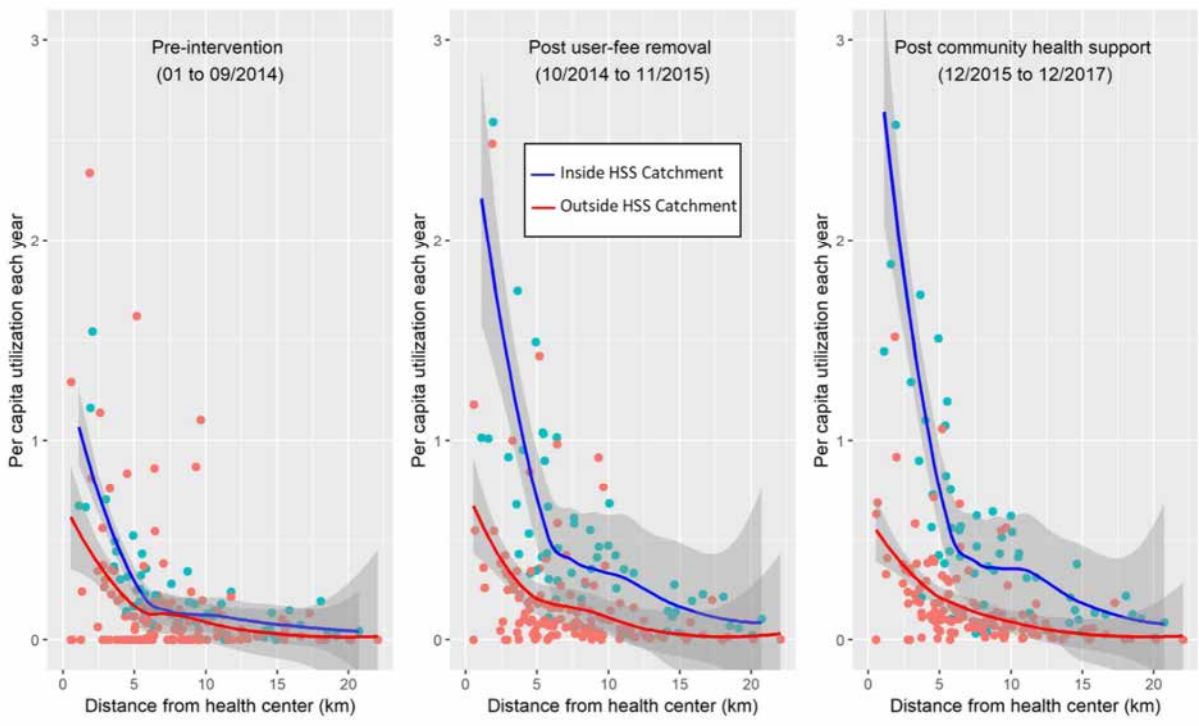

Figure 12. Average health facility utilization per capita in Ifanadiana District 2014-2017, by distance of each Fokontany to the nearest health facility. Colors represent the HSS-UHC intervention catchment (blue) and the rest of Ifanadiana district (red). Each dot represents one of the 195 Fokontany in Ifanadiana, solid lines are the respective non-linear smooth (local regression, LOESS method) and grey shades are the 95% confidence intervals around each smooth.

6. Future research

My current and future research activities build on the experience I have gained over the past ten years and the same principles that have shaped my early scientific career. Beyond a particular disease system, research method or field of study, I will strive to develop a solutions-oriented research agenda that helps understand pressing challenges in global health, improve health services or interventions aimed for vulnerable populations, and produce evidence for policy and scale-up when appropriate (Figure 13). In the next few pages, I summarize how I am trying to articulate this vision through some of my main research projects. First, I am expanding the work I began on infectious disease and geographic accessibility modelling, to produce e-health tools that can be useful to health actors and can be rapidly scaled over large geographical areas (*1. Building scalable e-health tools to improve health programs*). Second, I will continue conducting assessments of vertical and horizontal interventions, with a stronger focus on community health programs given the importance of geographic barriers to health care access in Madagascar and elsewhere (*2. Evaluation of novel health interventions and policies*). Finally, I will take advantage of my experience trying to understand feedbacks between environmental degradation, poverty and human health to contribute to projects that aim to operationalize "one health" or "planetary health" approaches on the ground in order to reduce zoonotic disease emergence and transmission (*3. Promoting and implementing integrated approaches for planetary health*). Most of this research is done with local teams, postdocs and students that I supervise directly and who allow me to expand my research agenda in multiple directions due to their wide range of backgrounds and expertise (medicine, health geography, disease ecology, etc.).

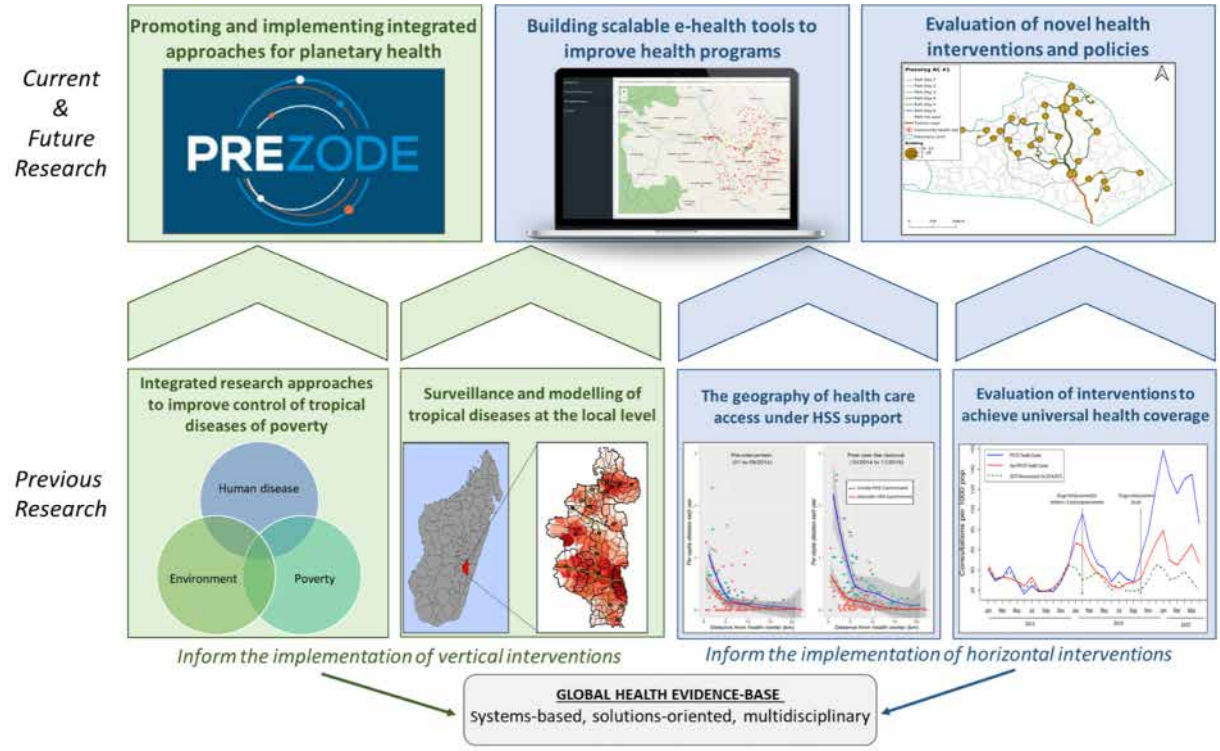

Figure 13. Evolution of my scientific agenda from previous research activities to current and future research. Schematics show my three main areas of current and future research, and how these relate to research carried out in the previous 10 years.

Building scalable e-health tools to improve health programs

Surveillance and control of malaria at the local level using e-health platforms

The poor performance of facility-based surveillance systems in areas of low healthcare access, a greater professionalization of CHW work through trainings in medical protocols and performance-based payment schemes, and the rise of mobile e-health platforms in the hands of CHWs for data collection and case management, have contributed to a strategic shift in how health system information is collected and used to inform health planning. Integration of feedback loops between infectious disease modelling approaches and existing community-based e-health platforms, can help to 1) plan efforts and resources necessary ahead of time for specific areas and periods, reducing stock-outs and increasing case detection; and 2) implement additional control activities that are predicted to minimize transmission at the population level. However, while such approaches are increasingly informing national or regional planning [127], their application at the local level, where intervention efforts actually take place, remains largely unexplored, especially in rural areas of sub-Saharan Africa [128]. Previous work I have done in Ifanadiana on surveillance, precision health mapping and modelling of infectious diseases have allowed me to recognize this gap, and build the foundations to start addressing this issue through a pilot study on malaria in collaboration with Pivot.

The goal of the project *"SMALLER: Surveillance and control of malaria at the local level using e-health platforms"* funded by ANR and for which I am the PI, is to develop statistical and mathematical models of malaria transmission that inform key features of program implementation, helping to adapt surveillance and control strategies at the community level. For this, we are coupling, at the level of a health district, accurate epidemiological surveillance of malaria cases, high resolution satellite information, and socio-economic data, to gain a comprehensive understanding of local malaria dynamics (Figure 14). Leveraging Pivot healthcare delivery platform and data collection systems in Ifanadiana, we will pilot innovative and reliable malaria decision-making tools that can be validated locally and scaled-up globally. The specific objectives of this project are 1) to estimate the unobserved burden of malaria at the community level for improved surveillance. Our hypothesis is that more than one third of symptomatic cases are unaccounted for in the district's facility-based surveillance system due to financial and geographical barriers to access healthcare; 2) to integrate community-level predictions of malaria transmission into existing CHW workflows in Ifanadiana district for improved program implementation. We hypothesize that the use of routine predictions of malaria cases at the community level by CHWs and supervisors can help improve case detection and reduce stock-outs of rapid diagnostic tests (RDTs) and antimalarial drugs; 3) to implement additional control strategies that minimize malaria transmission, informed by transmission model simulations. Our hypothesis is that implementation of malaria control activities based on a better understanding of local transmission can lead to further reductions of malaria incidence than blanket routine control strategies could achieve.

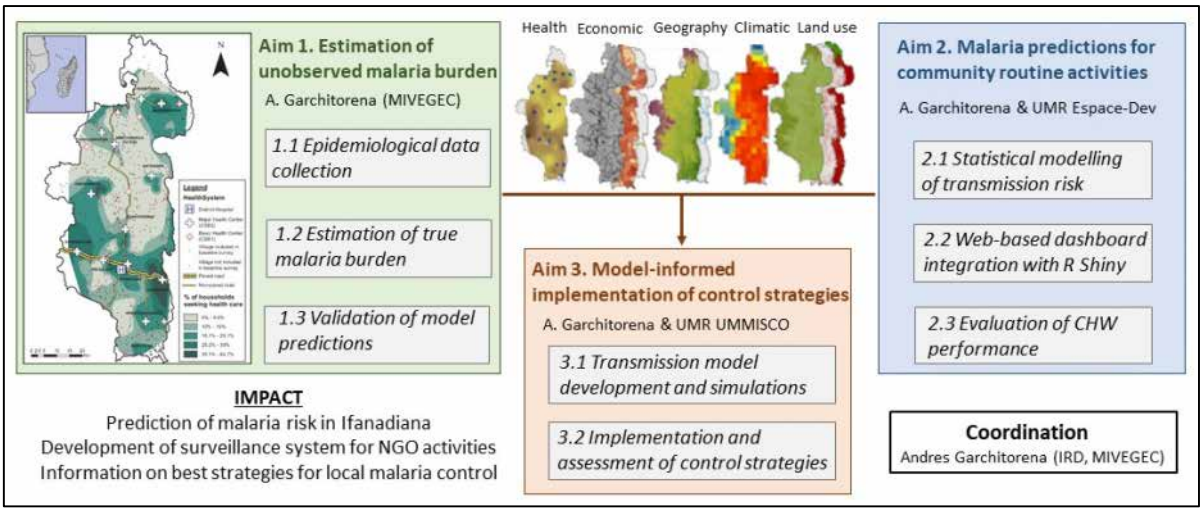

Figure 14. Schematic representation of the SMALLER project aims and organization

AIM 1. Estimate the unobserved burden of malaria at the community level to improve surveillance

The number of RDT confirmed malaria cases per month will be obtained for each of the 195 Fokontany (smallest administrative unit) in Ifanadiana district for 2015-2021. For this, the geographic information of each case will be retrieved from the registries of the 19 primary healthcare centres (~100,000 cases are expected based on 2015-2017 trends) and will be combined with CHW data at the Fokontany level. Since access to healthcare for febrile episodes is highly heterogeneous across the district due to substantial geographical and financial barriers [93, 94], we will use indirect estimation methods to capture the "hidden burden" of malaria cases. We will leverage our cohort's spatial data on healthcare access (80 clusters), together with geographical data on per capita utilization of non-malaria cases in order to correct raw information from the registries. For this, we will carry out benchmark-multiplier and multiple imputation methods, typically used in health systems research [129]. This work will allow us to obtain spatially accurate predictions of monthly malaria incidence at the local level for the period 2015-2021, which will be used in Aim 2 to identify associated factors. We will validate our model predictions of malaria spatio-temporal dynamics using point prevalence estimates of symptomatic malaria from a representative sample of Ifanadiana's population during the high malaria season of 2021. For this, we have included malaria RDTs in the 2021 wave of Pivot's cohort, which follows-up 1,600 households in Ifanadiana District (~8000 individuals), selected through a two-stage cluster-randomized design. All children under 15 years were tested and capillary blood was collected in filter papers for ulterior analyses.

AIM 2. Integrate community-level predictions of malaria transmission to improve routine activities

Detailed land use maps will be produced from high resolution satellite images to characterize known environmental factors that influence malaria transmission, using remote sensing techniques. This will allow the accurate mapping of settlements, agricultural fields, road networks, and footpaths to help measure anthropogenic gradients. Field observations will be conducted to refine image analyses and validate results. We will conduct a complementary temporal analysis using medium resolution images from Sentinel 1 and 2 satellites. This analysis will measure seasonal changes in vegetation, moisture and water (including floods) to characterize their impact on malaria dynamics. In addition, socio-economic data will be available through Pivot's cohort, including factors related with malaria exposure and vulnerability, such as bed net ownership and use, agricultural practices, poverty levels, malnutrition, or demography. We will combine GLMMs with spatial and time-series analyses to

estimate the influence of key drivers on the observed local malaria dynamics at the Fokontany level for 2015-2020. We will estimate the uncertainty around model estimates using multi-model selection algorithms [30]. Malaria data and models will be integrated into Pivot's systems for monitoring and evaluation to provide routine predictions of malaria transmission at the community level. For this, an interactive web-based interface will be created using package "Shiny" for R programming language and will be hosted at Pivot data platform [127]. We will automatize the extraction at frequent intervals of satellite environmental data (e.g. temperature, NDVI) and malaria incidence at the community level. Socio-economic data will be updated at every new wave of Pivot's cohort. Together, this will allow routine fitting of models to obtain updated spatio-temporal predictions that will be used by Pivot to plan in advance stocks of RDTs and antimalarial drugs for each CHW. Finally, we will assess whether the availability of malaria case predictions in CHW dashboards and supervisions helps reduce stock-outs (RDTs and antimalarial drugs) and increases case detection. For this, we will collect additional stock-out information at the community level before and after introduction of the dashboards. Since Pivot currently supports and supervises about half of the CHWs in the district (~200), the rest of CHWs will be used as a control group. We will carry out interrupted time-series analyses with control groups [93] to analyse its impact.

AIM 3. Model-informed implementation of control strategies to minimize malaria transmission

Relying on existing individual-based models that account for relationships between environment (climate, land use), mosquito dynamics, and disease transmission, we will fit a spatially explicit mathematical model to the observed spatio-temporal variations in malaria incidence [130]. This model, which will integrate key parameters and relationships relevant for Ifanadiana identified earlier (Aim 2), will allow us to simulate the impact of a range of interventions at the community level (e.g. active case detection, indoor spraying, bed-net distribution, awareness) targeted at specific periods and populations based on predicted patterns (e.g. hotspots during low transmission season), to assess which are the best strategies to minimize transmission [131]. Model-informed interventions will be discussed with Pivot's medical team and MoH district medical officer to assess their feasibility and buy-in. Implementation is expected to begin in the 2022-23 season and intervention impact will be assessed by comparing model predictions with observed trends in intervention and control groups. Feedbacks between research and medical teams during implementation phase will guide these efforts. Besides its scientific novelty, this project will represent an exemplary case for cross-sectoral collaboration between researchers, civil society and local governments for improving population health in low-resource settings.

Scaling tools for fine-scale geographic accessibility modelling

Widespread implementation of malaria control measures has resulted in a steady decrease of global incidence of malaria, but this trend has recently slowed and even reversed in some areas. Between 2016 and 2017, Madagascar saw an increase of more than half a million cases. Universal access to rapid diagnosis and treatment is a key strategy to reduce the burden of malaria, but access to health care remains low in rural areas of Madagascar, where over three quarters of the population live. For instance in 2016, only 15.5% of Malagasy children with reported fever had an RDT done and only 10.1% were treated with an antimalarial. Research I have led in Ifanadiana (described earlier) showed that poor geographic access to primary care in remote populations is one of the main factors driving low healthcare utilization, and support to community health programs is a key way to reduce geographic barriers to care, including for malaria. To optimize local malaria control interventions

targeted at remote populations and improve their access to malaria diagnoses and treatments, a very precise understanding of the local geography is necessary to identify populations with poor geographic accessibility to health facilities, plan field missions and set-up itineraries for community health workers (e.g. proactive care) and outreach teams (e.g. bed net distribution). However, implementation efforts are currently limited by a lack of basic geographic information (e.g. footpaths, residential areas, isolated households) in rural areas of Madagascar. Our pilot work in Ifanadiana on geographic access to care, where we combined a large-scale mapping project with novel geographic modelling methods and the development of e-health tools [121], has drawn the attention of international organisations such as USAID's President Malaria Initiative (PMI), who are interested in scaling these methods to other parts of Madagascar (Figure 15) in an attempt to inform the implementation of "last mile" interventions in partnership with the National Malaria Control Program of the MoPH.

The objective of the project "*Malaria remote populations (MRP): scaling tools for fine-scale geographic accessibility modelling in South Eastern Madagascar*" funded by USAID-PMI and for which I am the PI, is to scale-up work piloted in Ifanadiana to five other health districts in the area to develop very precise, context-specific estimates of geographic accessibility to care. This will help the MoPH and partner organizations with the design and implementation of interventions aimed at improving access for remote populations. As before, we will use a participatory approach on OpenStreetMap to map all the footpaths, residential areas and households in the five districts to accurately measure distance to health facilities for every single household in the study area. We will obtain corresponding travel time estimates, parametrized with prior fieldwork in Ifanadiana and remote sensing data analyses from high-resolution satellite images on the scale-up districts. Finally, we will integrate the results into a practical e-health platform for use by health actors. A web application will facilitate planning of activities, while a smartphone app will allow field teams get precise directions anywhere in their district. We will cross-validate our estimates of travel time to health facilities, comparing them with corresponding reported travel time obtained in a survey of over 1,600 households in Farafangana District. In addition, we will study the effect of access to health facilities on healthcare utilization and malaria incidence, combining information from health center registries and community health workers. The study is developed in collaboration with Institut Pasteur Madagascar, PMI Madagascar, USAID-ACCESS, Pivot and the National Malaria Control Program. The project will also be an opportunity to assess the feasibility, needs and costs related to scaling such comprehensive mapping projects and precise geographic accessibility modelling methods to larger areas of the developing world.

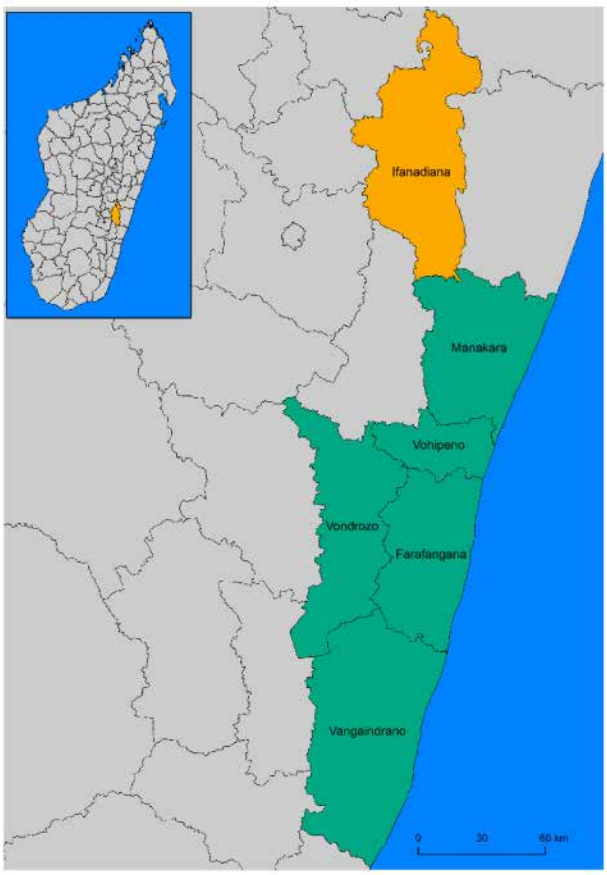

Figure 15. Scale-up of fine-scale geographic accessibility modelling in South Eastern Madagascar. Map shows in yellow the district of Ifanadiana, where the initial pilot was conducted, and in green the five other districts where the work is being scaled-up with funding from USAID.

Evaluation of novel health interventions and policies

Community health interventions to decrease malaria burdens

Given the pervasive effects of poor geographic access to health care and my experience on the subject during recent years, an important area of my current and future research is the evaluation of community health interventions in Madagascar, with a particular focus on malaria. In this sense, integrated community case management (iCCM) is one of the most common interventions implemented across sub-Saharan Africa. It utilizes CHWs to increase timely access to curative interventions for pneumonia, diarrhea and malaria, the main causes of death among children under 5 years of age in remote, vulnerable populations. Community-based testing and treatment for malaria, through iCCM, has demonstrated increases in treatment rates and care-seeking; and resultant reductions in severe malaria and malaria mortality in children under five years of age. There is growing interest among countries implementing iCCM in expanding access to all ages. Indeed, prompt care-seeking for fever has stagnated in a number of countries despite improvements in the availability of supplies and in the quality of care offered at health facilities. Anecdotal reports and some qualitative data suggest that where iCCM is implemented, communities may demand treatment for older age groups. Thus, expansion of malaria community case management (mCCM) to all ages may address some of the barriers to early care-seeking, including geographic distance and lack of time and resources to visit the nearest health facility, but the effectiveness of these efforts is unclear. To date, no studies have rigorously demonstrated the effectiveness of expanding mCCM to all ages in areas where malaria

prevalence remains moderate or high. This information is necessary to guide national health policies on the implementation of such an intervention in Madagascar and elsewhere.

The goal of the project "*Assessing the effectiveness of community case management of malaria (mCCM) for all ages in Farafangana District, Madagascar*", funded by USAID-PMI and implemented in close collaboration with the MoPH and the NGO Inter Aide, is to assess whether expanding mCCM to all ages increases the proportion of people of all ages who are tested for malaria by CHWs or at health facilities. The design of this pilot, for which I am co-PI, is a cluster-randomized trial with two arms (intervention and control) taking place in the catchment areas of 30 health facilities (15 per arm) comprising approximately 500 CHWs (Figure 16). In the control arm, case management of malaria by health facilities and CHWs is done in line with current national recommendations (iCCM for children <5 years). In the intervention arm, case management of malaria is done by health facilities and CHWs in line with current national recommendations (iCCM for children <5 years), with an extension of community case management of malaria to all ages. In both arms, the community health system is strengthened via trainings, sensitizations, routine supervisions and support to the supply management system.

Specific objectives of this project are to assess 1) whether expanding mCCM to all ages increases the proportion of household members with fever who sought care and, if tested positive for malaria, received treatment with an appropriate antimalarial, 2) whether expanding mCCM to all ages reduces the prevalence of malaria among children less than 15 years, 3) whether expanding mCCM to all ages affects the proportion of children under 5 years with illness seeking care for pneumonia and diarrhea, 4) the acceptability of the extension to all ages of mCCM, according to community members, CHWs, and health facility providers, and 5) the costs and cost-effectiveness of extending mCCM to all ages. In order to evaluate the effectiveness of the intervention, a cross-sectional household survey with a sample size of 1,680 households (840 per arm) will be carried out prior to the intervention and 24 months later. The survey will include a socio-demographic and questionnaire and health questions for all household members, answered by the head of household. In addition, a capillary blood sample will be taken from children under 15 years of age for a rapid diagnostic test and filter paper blood collection to understand the prevalence of malaria in this age group. Monthly quantitative data will be abstracted from the registers of health facilities and CHWs in the two arms and will be analysed for the entire study period. In addition, to better understand perceptions about the care offered in each arm, qualitative studies with community members, CHWs, and facility health workers will be conducted in both arms at the end of the intervention.

The expansion of mCCM to all ages being part of the Madagascar Malaria Strategic Plan 2018-2022, the study is set up as a pilot project in one endemic district prior to a national scale-up by the MoPH that will be supported by USAID-PMI and the Global Fund if the results are encouraging.

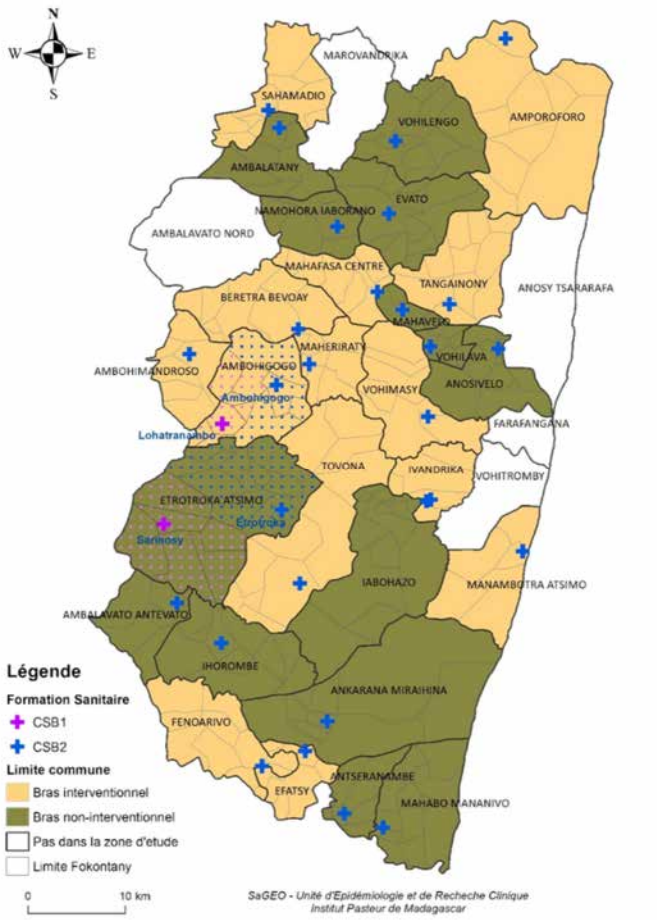

Figure 16. Study location and design of the mCCM project. The study is done in Farafangana District in the southeast of Madagascar, which corresponds to a moderate transmission zone (transmission levels during 2015-2017 were ~100 cases per 1,000 population based on passive surveillance). The 15 health center catchments in the control arm are shown in green and the 15 in the intervention arm are shown in yellow.

A multidisciplinary research agenda for adaptive HSS interventions

Most illness and death in developing countries are preventable and treatable with known solutions at costs that are affordable at scale. The challenges with scaling up these solutions are largely due to implementation: even simple technologies require complex delivery systems –a value chain of staff, stuff, systems, and space - to reach all patients. Rates of preventable disease and mortality remain high, in part, because of knowledge gaps due to poor alignment between research and health care delivery. My goal since I started collaborating with the NGO Pivot in Ifanadiana has been to progressively build a multidisciplinary research agenda around HSS that informs the MoPH-Pivot partnership locally, provides lessons for the government of Madagascar nationally and generates evidence for the global health community more broadly on HSS, UHC policies, and disease control interventions. As Pivot's Associate Scientific Director, I play a key role in setting the NGO's strategic priorities and I am responsible for leading an array of research projects, funded with internal or external resources on the following topics:

I. Population-level impact of HSS and UHC: Impact evaluation through analysis of a district-representative longitudinal cohort in combination with health system data has been foundational to my research in recent years. With each iteration of the HSS evaluation I include novel components, such as the spatio-temporal evolution of indicators, an analysis of geographic equity, and the development of an e-health tool for visualization of cohort results by programmatic teams in the last

wave of the IHOPE cohort. I will continue using these data to assess the impact of HSS and UHC in Ifanadiana, with an intervention that expands geographically, programmatically and adapts to the evidence produced by my research team. Given the longer time frame, in future analyses I will assess whether there are linear or non-linear changes in health care coverage indicators given Pivot's support, as well as the impact of the COVID-19 epidemic on health care seeking behaviors. Moreover, as the intervention will be soon scaled-up to other districts, we will aim to expand and adapt the IHOPE cohort accordingly to provide evidence on how the impact of HSS efforts changes during the scale-up phase.

II. Geographic equity in access to care: I will continue to develop new research in health geography to assess how a good understanding of the local geography can influence the provision of health care at every level of the health system in Ifanadiana District (community health, primary care, hospital). The platform for this will be the combination granular HMIS data (at the village level) with our massive GIS dataset containing over 100,000 buildings and 20,000 km of footpaths in Ifanadiana. At the community level, I will aim to characterize whether there exist geographic barriers even to community health use for children under 5, and whether proactive community health programs can help ensure universal access to care in remote areas. In addition, we will adapt "traveling salesman" algorithms (such as those used by home delivery companies) to characterize optimal routes for proactive CHWs to cover their catchment population and to inform programmatic needs in human resources according to geography. At the primary care level, I will aim to characterize how geographic access to maternal health services changes over time as a result of programs in place by the MoPH-Pivot partnership.

III. Health system analytics, eco-epidemiology and surveillance: As argued before, there exists an important gap in the application of current methods in eco-epidemiology to inform health system preparedness and disease control at local scales. My goal in this area is to develop new methods combining environmental information (e.g. remote sensing, vector surveillance), spatially granular health system information and population surveys, with models of disease transmission to understand and forecast local disease dynamics in Ifanadiana. Besides the project on malaria described in detail above, I will focus on other disease systems relevant to Ifanadiana, such as lymphatic filariasis, schistosomiasis, and COVID-19. Specifically, I will aim to characterize and understand the burden of disease at the community level, forecast local disease dynamics and integrate community-level predictions into tools for health workers that could improve activities. Moreover, I will aim to assess the expected impact of several disease control/elimination activities implemented in the district.

Promoting and implementing integrated approaches for planetary health

The emergence of new human and animal diseases is becoming more and more frequent at the global level, which is evidenced by the recent outbreaks of H5N1, EBOLA, Zika, or COVID 19. The majority of these emergences are of zoonotic origin, *i.e.* caused by pathogens of animal, domestic or wild origin. These emergences are deeply linked to the pressures exerted by humans on the environment such as deforestation, industrialization or pollution, and the associated negative impacts these have on ecosystem services and biodiversity. It is now recognized that the health of humans, animals and the environment are linked and that global frameworks of study and action (e.g. One Health, Eco-Health, or Planetary Health) are necessary to prevent or mitigate these emergences. The Global Initiative *"Preventing Zoonotic Disease Emergence (PREZODE)"* (https://prezode.org), announced by President Macron in the 2021 One Planet summit and endorsed by multiple international organizations, aims to promote these kinds global approaches in operational research in

order to prevent future pandemics. As a veterinarian with a background in public health and disease ecology, as well as field experience in implementation research, I am ideally positioned to contribute to this initiative, and I have been appointed IRD focal point for PREZODE in the Indian Ocean.

In this capacity, I will help develop in Madagascar over the next few years one of the first pilot projects of the PREZODE initiative funded by AFD in five priority countries. In collaboration with the SEGA-OI network – a regional health surveillance network led by the Commission for the Indian Ocean– the aim of the Madagascar pilot (for which I am co-PI) will be to develop and strengthen surveillance capacities for priority zoonotic diseases, such as Rift Valley fever and other vector-borne diseases, and those from pathogens originating in wildlife (e.g. Hantavirus, and Coronavirus) among others. Indeed, Madagascar has an exceptional number of endemic species, but intensive deforestation, poaching and slash-and-burn practices, in addition to climate change are all factors that can promote disease emergence. The project, which will be largely implemented in Ifanadiana District thanks to the strong partnership and knowledge we have around the area, will include three main pillars: (i) research activities allowing a better understanding, prediction and management of risk factors for zoonotic emergence, (ii) co-construction of ecosystems resilient to zoonotic risks with local actors, and (iii) the implementation of surveillance and early detection strategies adapted to the epidemiological contexts of the areas considered and to the practices and perceptions of local actors. In short, we will combine epidemiological studies with field collections to identify circulating pathogens, people at risk, community exposure and risks of exposure. This will make it possible to raise community awareness about these risks, and to induce changes in practices to reduce them. Finally, we will increase the capacity of surveillance systems already in place by integrating human, animal and environmental health surveillance at the community level in order to detect abnormal events early, which could lead to disease emergence.

As is the case with most of the projects I am involved with, the operational scope of the Madagascar pilot means that the project will be implemented via a collaboration between research institutions (CIRAD, IRD, IPM, Antananarivo University, Centre National de Recherche en Environnement), non-governmental organisations (Pivot, Agronomes et Vétérinaires sans Frontières, Centre Valbio, Wildlife Conservation Society) and government agencies (Direction de Veille Sanitaire Surveillance Epidémiologique et de Riposte, Direction des Services Vétérinaires).

7. Résumé en français

Contributions à la science

Plus d'un milliard de personnes, la plupart dans des pays tropicaux et subtropicaux, vivent encore dans l'extrême pauvreté et souffrent d'un fardeau disproportionné de maladies transmissibles [1, 2]. Les rétroactions entre la santé humaine et le développement économique ont contribué à une tendance positive au niveau global de la richesse et de la santé dans l'histoire récente, mais elles sont aussi en partie responsables des grandes inégalités présentes dans le monde aujourd'hui. Un lien important dans cette relation est le rôle de l'environnement sur les tendances spatiales historiques et actuels de pauvreté et de maladie [3–5]. Les régions tropicales ont des conditions climatiques et biologiques appropriées pour que les agents pathogènes se développent et persistent [6, 7], entraînant ainsi un fardeau important de maladies infectieuses et parasitaires qui nuisent à la productivité de leurs populations locales, entre autres impacts économiques [8, 9]. Dans le contexte actuel de dégradation de l'environnement, de changement climatique et d'occupation des sols, les régions tropicales et les populations vulnérables devraient supporter une charge disproportionnée d'effets néfastes sur la santé [10], ce qui exacerbera les inégalités existantes [11]. La reconnaissance de ces multiples liens (figure 1) a favorisé un engagement multilatéral global en faveur du développement humain, du bien-être et de la préservation de l'environnement, incarné dans les objectifs de développement durable (ODD) [12]. Alors que les ODD guident les politiques et l'aide au développement sur tous ces fronts au cours de la période 2015-2030, il est nécessaire de disposer de cadres d'étude et d'action intégratifs, multidisciplinaires et basés sur des systèmes, afin de s'attaquer à certains des problèmes les plus urgents du développement durable aujourd'hui.

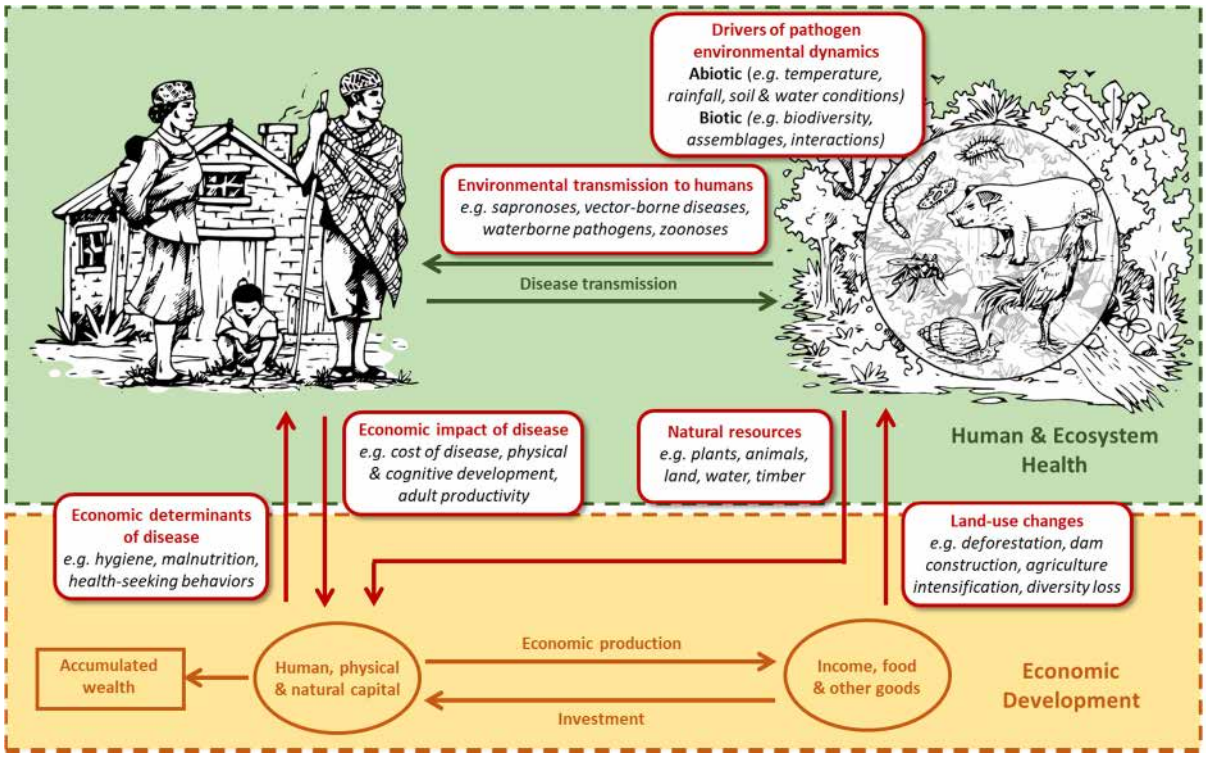

Figure 1. Rétroactions entre écosystèmes, maladies infectieuses et développement économique [13].

Mon expérience multidisciplinaire avant de devenir chercheur à l'Institut de Recherche pour le Développement (IRD) m'a aidé à mieux comprendre comment ces interactions entre la pauvreté, la dégradation de l'environnement et les maladies humaines se déroulent dans des contextes réels et comment des solutions peuvent être mises en œuvre pour y remédier sur la base de ces connaissances.

Après avoir terminé 5 ans de formation de médecin vétérinaire à l'Université « Complutense de Madrid », j'ai réalisé un Master Européen en Santé Publique (2009-2011) au cours duquel j'ai acquis de l'expérience grâce à des stages auprès du Ministère guatémaltèque de la Santé Publique sur la lutte contre les maladies à transmission vectorielle, et avec le Réseau Villes-Santé Français de l'OMS sur les déterminants sociaux de la santé et la santé urbaine. Ces compétences biomédicales, combinées à des connaissances en santé environnementale et en déterminants sociaux de la santé, m'ont permis de développer un projet de doctorat multidisciplinaire financé par le réseau doctoral Français en Santé Publique. Mon doctorat, réalisé en 2011-2014 sous la supervision des écologistes Jean François Guégan et Benjamin Roche (IRD), visait à évaluer les interactions entre la pauvreté, les facteurs environnementaux et l'ulcère de Buruli, en combinant un travail de terrain écologique approfondi au Cameroun avec des analyses de modélisation statistique et mathématique. De 2015 à 2017, j'ai été postdoc en santé mondiale et médecine sociale à la Harvard Medical School, supervisée par l'économiste Matthew Bonds et l'épidémiologiste Megan Murray. Au cours de la même période, je suis devenu responsable de recherche pour l'ONG Pivot, fondée par Matthew Bonds en 2014 et basée à Madagascar, où j'ai passé la plupart de mon temps. Au cours de cette période, j'ai concentré mes recherches sur une meilleure compréhension des inégalités en matière de santé et sur la réalisation d'évaluations d'impact des interventions sanitaires dans le cadre du programme de renforcement des systèmes de santé (RSS) de Pivot dans le district d'Ifanadiana, à Madagascar.

Cet ensemble divers d'expériences et d'intérêts de recherche a fortement façonné mon programme, mes approches et mes contributions scientifiques. Tout d'abord, les méthodes en écologie et en économie des maladies que j'ai apprises au cours de mon doctorat et de mon postdoctorat m'ont permis de développer des approches de recherche pour comprendre, d'un point de vue théorique et empirique, comment la prise en compte simultanée de la dynamique environnementale des agents pathogènes, de la dynamique économique et de la santé humaine peut aider à éclairer les activités de contrôle des maladies (Section 1. Approches de recherche intégrées pour améliorer le contrôle des maladies tropicales de la pauvreté). Deuxièmement, mon expérience en Ifanadiana m'a fait réaliser que, bien qu'il y ait eu des progrès incroyables dans la modélisation des maladies infectieuses dans la littérature universitaire, ces méthodes sont rarement utilisées d'une manière qui informe la mise en œuvre des activités de contrôle au niveau local. J'essaie de combler cette lacune en adaptant les méthodes de collecte de données et les analyses pour un certain nombre de maladies pertinentes dans la région afin que les résultats de la recherche puissent être utilisés par les acteurs locaux de la santé (Section 2. Surveillance et modélisation des maladies tropicales au niveau local). Troisièmement, même si la compréhension des déterminants écologiques et socio-économiques de la santé peut mener à de meilleures stratégies verticales de prévention et de contrôle des maladies, j'ai pris conscience du potentiel que les approches horizontales en santé, telles que le RSS, les interventions et les politiques de couverture sanitaire universelle (CSU), ont pour améliorer durablement la santé des populations. Mes recherches sur ce front se sont concentrées sur la mise en place de méthodes robustes de collecte des données et d'évaluation (observationnelles, quasi expérimentales) pour mesurer l'impact de telles approches et éclairer leur mise en œuvre (3. Évaluation des interventions visant à atteindre la couverture sanitaire universelle). Enfin, comme mes travaux de recherche sur la mise en œuvre ont constamment révélé la persistance des inégalités géographiques au fil du temps, les approches de géographie de la santé sont apparues comme une expansion nécessaire de mon programme de recherche, où j'essaie de caractériser précisément les inégalités géographiques dans l'accès potentiel et réalisé aux soins de santé à différents niveaux de soins (4. La géographie de l'accès aux soins de santé dans le cadre du soutien du RSS).

Approches de recherche intégrées pour améliorer le contrôle des maladies tropicales de la pauvreté

Mon premier intérêt de recherche portait sur les interactions entre la pauvreté, les facteurs de risque environnementaux et l'émergence ou la persistance de maladies infectieuses, inspirés par des travaux antérieurs sur les pièges de pauvreté induits par les maladies infectieuses [5, 14, 15]. En ce sens, les maladies tropicales négligées (MTN), un groupe de maladies chroniques, défigurantes et invalidantes, représentent un cas d'étude parfait de fortes rétroactions écologiques et économiques avec les maladies humaines. La persistance environnementale de bon nombre de ces maladies, combinée à un lien étroit avec la pauvreté, signifie qu'une diminution réussie et durable du fardeau de nombreuses MTN nécessite une compréhension plus large des interactions qui ont lieu entre systèmes humains et environnementaux.

Mon travail dans ce domaine a commencé pendant mon doctorat, où j'ai étudié ces interactions dans le contexte d'une seule maladie, l'ulcère de Buruli, afin de mieux comprendre les facteurs écologiques conduisant à un risque d'infection plus élevé, son mode de transmission à l'homme et ses impacts économiques dans les zones endémiques. Mon doctorat visait à fournir des informations sur les mécanismes écologiques permettant à *M. ulcerans* de croître, de persister et d'être transmis de l'environnement à l'homme, en utilisant une approche multidisciplinaire et de terrain au Cameroun (Figure 2). Pour cela, j'ai caractérisé la dynamique écologique de *M. ulcerans* avec des détails sans précédent dans de multiples communautés aquatiques de deux régions endémiques de l'ulcère de Buruli pendant un an [29]. On a constaté que *M. ulcerans* se développait pendant les périodes de précipitations intensives, et que des conditions physico-chimiques optimales dans les écosystèmes lentiques (c.-à-d. faible débit d'eau, faible teneur en oxygène, pH légèrement acide, température élevée) favorisaient la persistance environnementale de l'agent pathogène et la colonisation des hôtes aquatiques [30].

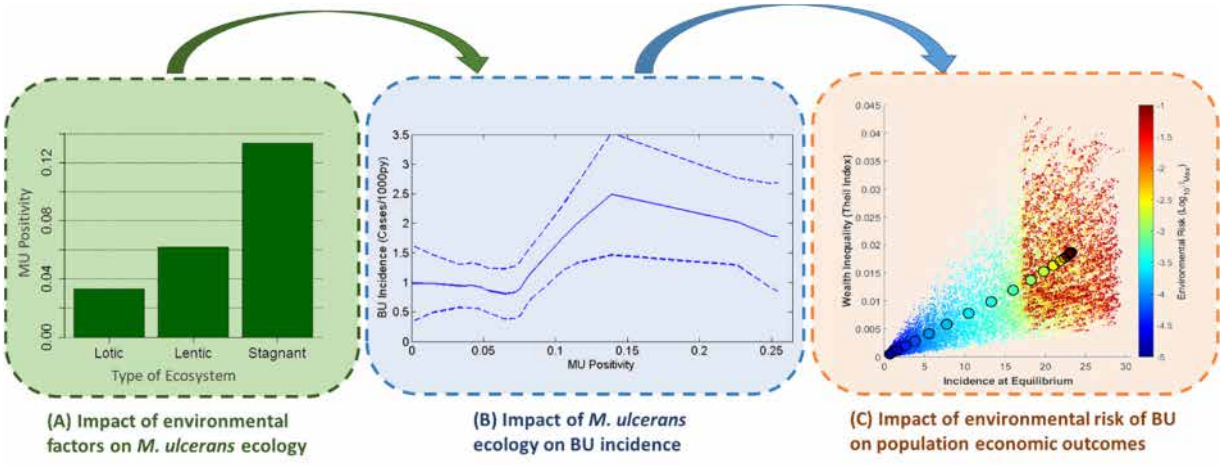

Figure 2. Rétroactions entre environnement, l'ulcère de Buruli et le développement économique. (A) La prévalence de la bactérie dans les sites aquatiques a été favorisée par des conditions spécifiques dans les écosystèmes stagnants et à débit lent (lentique) [30]. (B) Les schémas spatiaux et temporels de l'ulcère de Buruli (axe des y) ont été influencés par la prévalence environnementale de M. ulcer*ans* (axe des x) [34]. (C) Augmentation des inégalités de richesse (axe des y) en fonction de l'incidence des BU (axe des x) et de la charge environnementale de *M. ulcerans* (gradient de couleur) [35].

Nous avons associé par modélisation mathématique ces dynamiques environnementales de *M. ulcerans* aux modèles d'incidence de l'ulcère de Buruli dans les populations humaines dans les deux

régions endémiques, ce qui a fourni la première preuve sur le terrain qu'une transmission environnementale à l'homme est susceptible de jouer un rôle plus important qu'une transmission vectorielle dans les zones endémiques, et suggéré que la charge environnementale de *M. ulcerans* pourrait prédire à l'avance les tendances temporelles et spatiales de l'incidence de l'ulcère de Buruli [34]. Afin de comprendre l'impact des écosystèmes à haut risque sur l'émergence des cas d'ulcère de Buruli et sur le développement économique des populations touchées, nous avons développé un modèle économico-épidémiologique qui incorporait un gradient de risque environnemental [35] et les disparités dans la vulnérabilité à l'ulcère de Buruli et dans l'accès au traitement en tant que fonctions des ressources économiques dans un modèle de maladie. Nous avons montré que, pour les maladies tropicales rares mais très invalidantes comme l'ulcère de Buruli, une combinaison de rétroactions environnementales et socio-économiques peut entraîner d'importantes inégalités au niveau de la population, avec des impacts disproportionnés sur les groupes socio-économiques les plus pauvres [35].

Au cours de mon postdoctorat, j'ai continué à explorer le genre de cadres de modélisation intégrée que j'avais commencé avec l'ulcère de Buruli, mais avec des applications plus larges pour le contrôle d'autres maladies tropicales de la pauvreté. Grâce à une collaboration avec mon superviseur Matthew Bonds, Giulio de Leo (Université de Stanford) et d'autres modélisateurs de maladies infectieuses, nous avons adapté des modèles de pièges de pauvreté pour mieux comprendre comment les maladies dans un spectre différent de persistance environnementale pourraient affecter le succès des stratégies classiques de contrôle, et comment cela pourrait avoir un impact sur la dynamique économique au niveau de la population [13]. Nous avons montré que pour les maladies de transmission directe et celles transmises par l'environnement avec des nombres de reproduction de base comparables, le contrôle peut être plus efficace pour les maladies directement transmissibles grâce à des traitements médicaux périodiques. En plus de ce travail, une collaboration avec les chercheurs vétérinaires Cassidy Rist et Tom Gillespie (Université d'Emory) a permis à notre groupe d'adapter un cadre intégré similaire pour étudier comment les maladies du bétail peuvent avoir un impact sur la santé et la richesse des ménages ruraux pauvres, à la fois d'un point de vue théorique et empirique [43, 44]. Nos modèles suggèrent que les ménages peuvent perdre jusqu'à un quart de leur revenu mensuel dans les conditions de maladie locales existantes, ce qui plaide en faveur d'un soutien plus fort aux programmes vétérinaires qui ciblent les maladies courantes du bétail [44].

Surveillance et modélisation des maladies tropicales au niveau local

La quantité croissante de données disponibles, en combinaison avec des méthodes robustes d'estimation spatio-temporelle de l'incidence des maladies et des taux de couverture des interventions peuvent éclairer les politiques de contrôle et leur mise en œuvre. Cependant, il existe un écart substantiel entre nos capacités d'analyse collective et l'utilisation de ces capacités pour résoudre les problèmes là où ils comptent le plus – dans les zones d'extrême pauvreté avec des charges de morbidité élevées. Pour que les approches de modélisation conduisent à des interventions efficaces, les relations entre les maladies et leurs facteurs de risque socio-écologiques observées a des grades échelles doivent rester aux résolutions spatiales fines pertinentes pour les acteurs de la santé publique qui mettent en œuvre les activités de contrôle. Mon travail depuis 2015 avec l'ONG Pivot dans le district d'Ifanadiana (Madagascar) m'a poussé à tenter d'adapter ces méthodes, qui sont courantes dans la recherche en écologie des maladies infectieuses, mais d'une manière qui peut être utile aux acteurs de santé travaillant à l'échelle locale.

Tout d'abord, avec Michelle Evans, doctorante à l'Université de Géorgie à Athens (laboratoire de John Drake) que j'ai supervisé lors d'un stage à Ifanadiana, nous avons exploré si les associations environnementales à grande échelle pour les maladies diarrhéiques étaient applicables en Ifanadiana pour aider à éclairer la mise en œuvre programmatique. Pour cela, nous avons utilisé plusieurs ensembles de données spatio-temporelles de maladies diarrhéiques infantiles dans le district d'Ifanadiana collectés au niveau du village et de la commune sur 5 ans [59]. Dans notre zone d'étude, seules les variables socio-économiques, qui ont de faibles signatures spatiales, étaient des prédicteurs importants des modèles spatiaux de la maladie. Nos modèles ont globalement mal fonctionné, ce qui limite leur utilisation opérationnelle pour le ministère de la Santé, Pivot ou d'autres acteurs de la santé à ces échelles. Malgré ces résultats, nous travaillons sur une cartographie et une modélisation précises de la santé au niveau local pour d'autres systèmes pathologiques, tels que le paludisme, afin de voir si l'incidence plus élevée, de meilleurs rapports et (probablement) des signatures environnementales plus fortes nous permettent de prédire de manière plus fiable la dynamique de la maladie. Cependant, cela nécessite des améliorations dans la précision et la résolution spatiale des données de surveillance de routine. Pour cela, avec Elizabeth Hyde, étudiante en médecine à l'Université de Stanford que j'ai supervisé lors d'un stage à Ifanadiana, nous avons utilisé un ensemble de données de patients géo référencées de près de 300 000 consultations et 75 000 cas de paludisme diagnostiqués dans les centres de santé du district sur quatre ans. Nous avons ajusté l'incidence du paludisme au niveau du village à l'aide d'un indice d'utilisation des soins de santé, que nous avons obtenu en suivant un modèle spatio-temporel précis des déterminants locaux de l'accès aux soins de santé [70]. À l'aide de multiples critères de validation croisée, y compris des comparaisons avec une cohorte longitudinale représentative du district, nous montrons que nos estimations sont moins sensibles aux barrières géographiques dans l'accès aux soins ou aux changements soudains dans l'accès financier en raison des programmes de gratuité des soins mises en place pendant la période d'étude [70]. Nous avons montré que la surveillance passive manquait environ 4 cas de paludisme sur 5 et ne détectait pas les « hotspots » spatiaux à forte transmission du paludisme dans le district.

En ce qui concerne les travaux empiriques menés en Ifanadiana pour améliorer le contrôle local des maladies tropicales, j'ai continué à m'intéresser aux MTN, dans ce cas via l'étude des programmes d'élimination de la filariose lymphatique. En collaboration avec la responsable du Programme national, Holivololona Rabenantoandro et l'étudiante malgache M2 Estelle M. Raza-Fanomezanjanahary, nous avons réalisé la première enquête d'évaluation de la transmission en milieu scolaire (TAS en anglais) dans l'île, en plus de deux enquêtes communautaires simultanées chez les enfants et les adultes (~6 000 personnes), afin d'évaluer la transmission de la filariose lymphatique dans quatre districts sanitaires du sud-est de Madagascar. Le TAS chez les enfants scolarisés est l'outil recommandé par l'OMS pour aider les programmes nationaux à décider où la distribution de masse de médicaments peut être arrêtée [72], mais la validité de leurs conclusions a rarement été évaluée. La multiplicité de ces enquêtes nous a permis de montrer que, bien que trois de ces districts étaient éligibles à l'interruption de la distribution de masse des médicaments sur la base des résultats du TAS, la prévalence chez les adultes est restée remarquablement élevée même après dix ans de distribution de masse des médicaments [74]. Notre étude a suggéré que des différences dans les stratégies de distribution et l'adhérence chez les enfants scolarisés et les adultes pourraient être à l'origine de ces résultats contradictoires.

Évaluation des interventions visant à atteindre la couverture sanitaire universelle

Malgré l'importance des programmes verticaux pour contrôler ou éliminer des maladies particulières, les objectifs de développement durable (ODD) reflètent l'importance d'investir dans les systèmes de soins de santé primaires pour améliorer la santé de la population en mettant l'accent sur des approches sectorielles, telles que le renforcement des systèmes de santé (RSS) et la couverture sanitaire universelle (CSU). L'OMS a estimé que pour atteindre les ODD liés à la santé, près des trois quarts de tous les investissements supplémentaires requis pour les pays à revenu faible et intermédiaire au cours de la période 2015-2030 devraient être alloués au RSS, à la CSU et à d'autres approches sectorielles (figure 7), soit environ 300 milliards par an d'ici 2030 [77]. Un changement aussi radical des priorités exige une refonte profonde de l'évidence scientifique nécessaire et des méthodologies d'évaluation appropriées pour éclairer l'allocation et la mise en œuvre des fonds, car la base scientifique actuelle pour éclairer cette intégration horizontale est insuffisante [76, 78, 79]. En ce sens, l'un des principaux objectifs de mes recherches a été de développer des méthodes robustes de collecte des données et d'évaluation (observationnelles, quasi-expérimentales) en parallèle d'une intervention RSS-CSU mise en œuvre dans le district d'Ifanadiana.

Mes recherches montrent que le faible accès aux soins de santé au départ de l'intervention RSS-CSU en Ifanadiana était associé à des obstacles financiers et géographiques, et que la gratuité des soins mise en œuvre en 2014 a eu des impacts immédiats et importants sur l'utilisation des soins de santé primaires [93]. Les résultats des vagues ultérieures de la cohorte ont révélé des améliorations substantielles dans la recherche de soins et les inégalités économiques, deux objectifs centraux des politiques de CSU [94, 95]. De 2014 à 2018, la couverture a augmenté de plus de 4 % par année pour les soins des maladies des enfants et des adultes et pour les accouchements en centre de santé (figure 8), même dans les groupes économiques les plus pauvres. Malgré l'amélioration de la zone d'intervention dans tous les indicateurs de couverture et de mortalité évalués, les différences avec le reste du district pour la couverture des soins maternels et les taux de mortalité de moins de 5 ans étaient modestes [94, 95]. Cela pourrait être associé à des inégalités géographiques persistantes dans l'accès aux soins observées dans la zone d'intervention au cours de la période d'étude. Nos résultats fournissent des preuves convaincantes des effets des interventions de RSS-CSU au niveau de la population, mais mettent également en garde contre les lacunes dans les soins qui peuvent persister à moins que les systèmes de santé ne renforcent adéquatement les programmes de santé communautaire pour les populations enclavées.

Bien que l'augmentation de l'utilisation et de la couverture des soins de santé soit importante, il est essentiel d'assurer également la prestation de soins de haute qualité pour améliorer la santé de la population. En collaboration avec Camille Ezran, étudiante à l'Université de Stanford que j'ai supervisée pour son M2, nous avons examiné les changements dans le contenu des soins pour la mère et l'enfant au cours des deux premières années (2014-2016) de l'intervention RSS-CSU en Ifanadiana, en tant que proxy de la qualité des soins. À l'aide d'informations provenant d'enquêtes de la cohorte IHOPE ainsi que d'enquêtes « Service Availability and Readiness Assessments (SARA) » dans les établissements de santé, nous avons constaté que l'intervention entraînait une augmentation générale de la prestation des services santé recommandés par l'OMS, tels que les prescriptions de médicaments, les tests diagnostiques et les conseils [102]. Nous avons également cerné des lacunes précises dans la qualité des services offerts. Un autre déterminant clé de la santé de la population, outre la couverture et la qualité des interventions curatives, est la prestation d'interventions préventives telles que la vaccination des enfants. Sur ce front, j'ai travaillé avec Elinambinina Rajaonarifara, doctorante

malgache que je co-supervise avec Benjamin Roche (UMR MIVEGEC), pour évaluer comment le RSS peut aider à améliorer la couverture vaccinale, via ses impacts sur la vaccination de routine notamment. En utilisant des données au niveau du système de santé et de la population en Ifanadiana, nous avons montré que l'intervention RSS entraînait une augmentation des vaccinations de routine, ce qui entraînait une couverture vaccinale plus élevée, une réduction des inégalités économiques et une proportion plus élevée de vaccinations à temps [103]. Toutefois, les gains observés ont profité de façon disproportionnée à ceux qui pouvaient accéder le plus facilement aux services, ce qui a entraîné une persistance des inégalités géographiques dans la région qui ont empêché l'atteinte des objectifs de couverture internationale pour de nombreux groupes de population (figure 3).

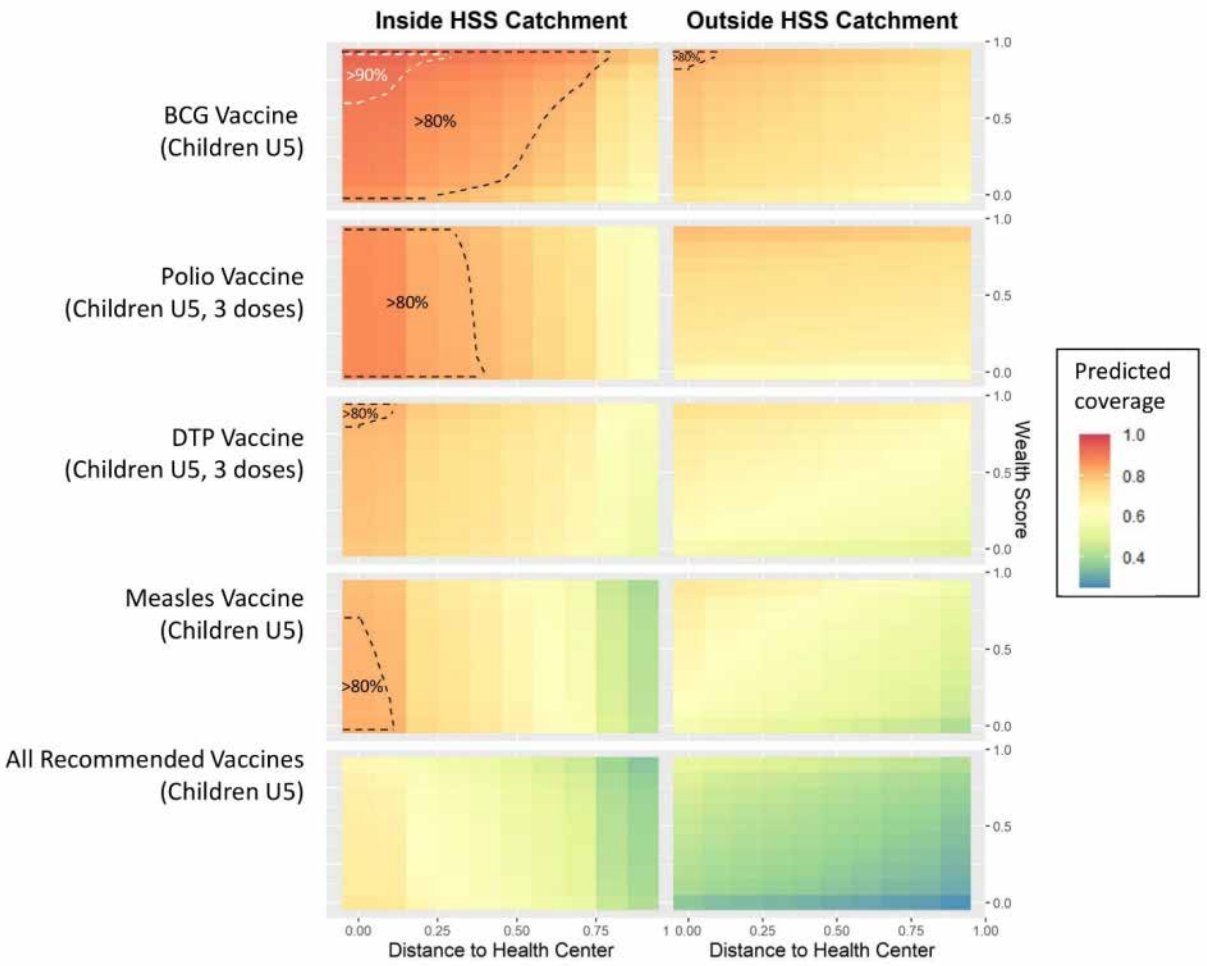

Figure 3. Prédictions pour atteindre les objectifs de couverture vaccinale pour différents groupes de population dans le district d'Ifanadiana. Prédictions de couverture vaccinale pour l'année 2018 dans chaque zone d'intervention, estimées à partir des modèles sur les données de la cohorte IHOPE 2014-2018 [103].

La géographie de l'accès aux soins de santé dans le cadre du soutien du RSS

Un thème commun à la plupart de mes recherches à Ifanadiana a été la persistance des inégalités géographiques dans l'accès aux soins de santé malgré les interventions mises en place pour améliorer l'accès financier et la qualité des soins. En effet, un faible accès géographique aux soins de santé peut constituer un grand obstacle à la réalisation de la CSU, qui est censée rendre les services de santé accessibles et abordables « pour tous, partout ». L'utilisation des soins primaires diminue de façon exponentielle pour les populations vivant à une distance croissante des services de santé [64–68]. Cette diminution d'accès liée à la distance est équivalente à l'effet des couts directs d'utilisation des soins [109], qui peuvent être réduits ou éliminés plus directement grâce aux politiques de CSU [104–108]. Il existe de nombreuses solutions potentielles pour améliorer l'accès géographique à différents niveaux de soins, mais elles nécessitent toutes une compréhension détaillée de barrières géographiques locales à l'accès aux soins de santé à chaque niveau de soins. Dans un contexte où des efforts RSS sont en place et visent à améliorer l'accès aux soins de santé pour tous dans le cadre des projets pilotes de la CSU de Madagascar, mes recherches à Ifanadiana se sont donc concentrées sur i) le développement de méthodes qui nous permettent de comprendre l'accès géographique aux soins avec suffisamment de précision pour être informatif sur les acteurs locaux de la santé, et ii) l'évaluation des stratégies potentielles ou actuelles pour réduire les barrières aux soins dans la population, et comment ils affectent l'accès géographique.

Tout d'abord, en collaboration avec la chercheuse postdoctorale malgache Felana Ihantamalala, nous avons développé de nouvelles méthodes pour obtenir des estimations très précises de l'accessibilité géographique aux soins en Ifanadiana afin d'aider Pivot et le ministère de la Santé à concevoir et à mettre en œuvre des interventions qui améliorent l'accès des populations enclavées [121]. Nous avons utilisé une approche participative sur OpenStreetMap pour cartographier plus de 20 000 km de sentiers pédestres et 100 000 bâtiments afin de mesurer avec précision la distance aux établissements de santé et aux sites communautaires pour chaque ménage du district via l'outil Open-Source Routing Machine (ORSM) (figure 4). Nous avons obtenu des estimations de temps de trajet correspondantes, paramétrées avec des centaines d'heures de travail sur le terrain et d'analyses de données de télédétection, et nous avons intégré tous ces résultats dans une plate-forme pratique d'e-santé à l'usage des acteurs locaux. Nous avons montré que la proportion de la population d'Ifanadiana ayant un accès géographique limité aux établissements de santé est beaucoup plus importante que ce qui est généralement rapporté ailleurs [120]. En utilisant une approche similaire, nous avons recueilli des informations sur 70 000 km de déplacements motorisés par des véhicules de l'ONG (voitures, motos) en Ifanadiana afin d'obtenir des estimations du temps de référence (des centres de santé à l'hôpital, en véhicule motorisé) et du temps pré-hospitalier (en ajoutant le trajet à pied de chaque ménage du district au centre de santé le plus proche) [122]. Nous avons montré qu'environ 10% de la population vivait à moins de deux heures de l'hôpital et plus de la moitié vivait à plus de quatre heures. Si ces résultats locaux sont représentatifs des tendances plus larges pour l'Afrique subsaharienne, ils pourraient avoir des implications majeures pour les politiques internationales de santé qui tentent d'atteindre l'objectif que 80% de la population puisse accéder à un hôpital dans les 2 heures [124].

Deuxièmement, bien que l'effet des obstacles géographiques à l'accès aux soins de santé ait été abondamment étudié et que la diminution dans l'accès aux soins de santé liée a la distance ait été caractérisée dans de multiples contextes [64–68], il existe peu de recherches sur la façon dont les changements dans le système de santé liées au RSS et CSU peuvent impacter la géographie de l'accès aux soins, laissant les politiques qui sont censées assurer l'accès pour tous être aveugles à leurs effets

sur les populations enclavées. Pour répondre à cette question, nous avons recueilli les lieux de résidence de près de 300 000 patients vus dans tous les établissements de soins de santé primaires du district entre 2014 et 2017 afin d'évaluer les changements spatio-temporels des taux de consultation au niveau fokontany (plus petit niveau administratif) à la suite de l'intervention RSS-CSU. Nos résultats montrent qu'en dépit d'un triplement des taux d'utilisation au cours de la période d'étude, l'utilisation a considérablement diminué au cours des 5 premiers kilomètres, même après le renforcement des centres de santé et la gratuité des soins. Cependant, combinées à des programmes de santé communautaire renforcés, ces politiques peuvent avoir des répercussions importantes sur la portée géographique du système de santé, car les soins des agents communautaires dans notre contexte ont permis aux enfants de moins de 5 ans d'atteindre au moins 2 consultations par année, quelle que soit leur distance aux centres de santé [125]. Nous avons également étudié comment la géographie locale peut limiter l'impact d'un programme de références hospitalières renforcé mis en œuvre dans le district, en termes de nombre de références complétés [122], montrant que dans notre contexte, le temps de référence est resté le principal obstacle limitant le nombre de références malgré les efforts du RSS. L'ajout de deux nouveaux centres de référence a été estimé à tripler la population vivant à moins de deux heures d'un centre avec une meilleure capacité de soins d'urgence et presque doubler le nombre de références attendues. Ensemble, nos études ont démontré comment les interventions RSS-CSU peuvent être optimisées pour l'accessibilité géographique à l'échelle locale.

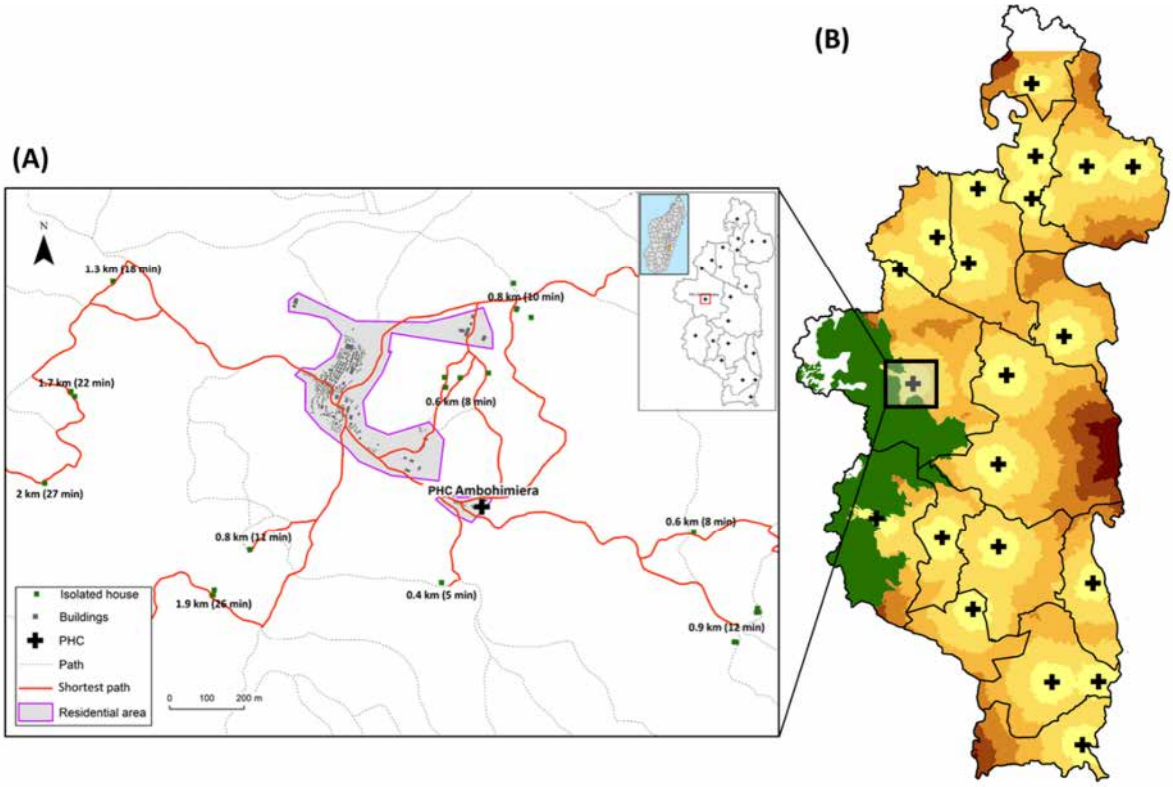

Figure 4. Estimation de la distance et du temps de trajet des ménages aux établissements de santé. (A) Montre un exemple illustratif des chemins les plus courts obtenus selon osrm, avec des prédictions pour la distance et le temps nécessaire pour atteindre l'un des SSP du district. (B) Affiche les cartes résultantes du temps de trajet pour tous les ménages du district d'Ifanadiana, qui varient de moins de 1 h (jaune) à plus de 5 h (brun) [121].

Recherches futures

Mes activités de recherche actuelles et futures s'appuient sur l'expérience que j'ai acquise au cours des dix dernières années et sur les mêmes principes qui ont influencé mon début de carrière scientifique. Au-delà d'un pathogène, d'une méthode de recherche ou d'un domaine d'étude particulier, je m'efforcerai d'élaborer un programme de recherche axé sur des solutions concrètes et qui aide à mieux comprendre des défis en matière de santé mondiale, à améliorer les services de santé sur le terrain ou les interventions destinés aux populations vulnérables, ainsi qu'à produire des preuves pour leur mise à l'échelle. J'essaie d'articuler cette vision à travers certains de mes principaux projets de recherche. Tout d'abord, j'élargis le travail que j'ai commencé sur la modélisation des maladies infectieuses et de l'accessibilité géographique, afin de produire des outils e-santé qui peuvent être utiles aux acteurs locaux et qui peuvent être étendus à d'autres zones géographiques (1. Développement d'outils e-santé pour améliorer les programmes de santé). Deuxièmement, je continuerai à effectuer des évaluations d'interventions verticales et horizontales, en mettant davantage l'accent sur les programmes de santé communautaire compte tenu de l'importance des barrières géographiques à l'accès aux soins à Madagascar et ailleurs (2. Évaluation de nouvelles interventions et politiques en matière de santé). Enfin, je profiterai de mon expérience de recherche sur les liens entre dégradation de l'environnement, pauvreté et santé humaine pour contribuer à des projets qui visent à opérationnaliser des approches « une seule santé » ou « santé planétaire » sur le terrain afin de réduire l'émergence et la transmission de zoonoses (3. Promotion et mise en œuvre des approches intégrées pour la santé planétaire).

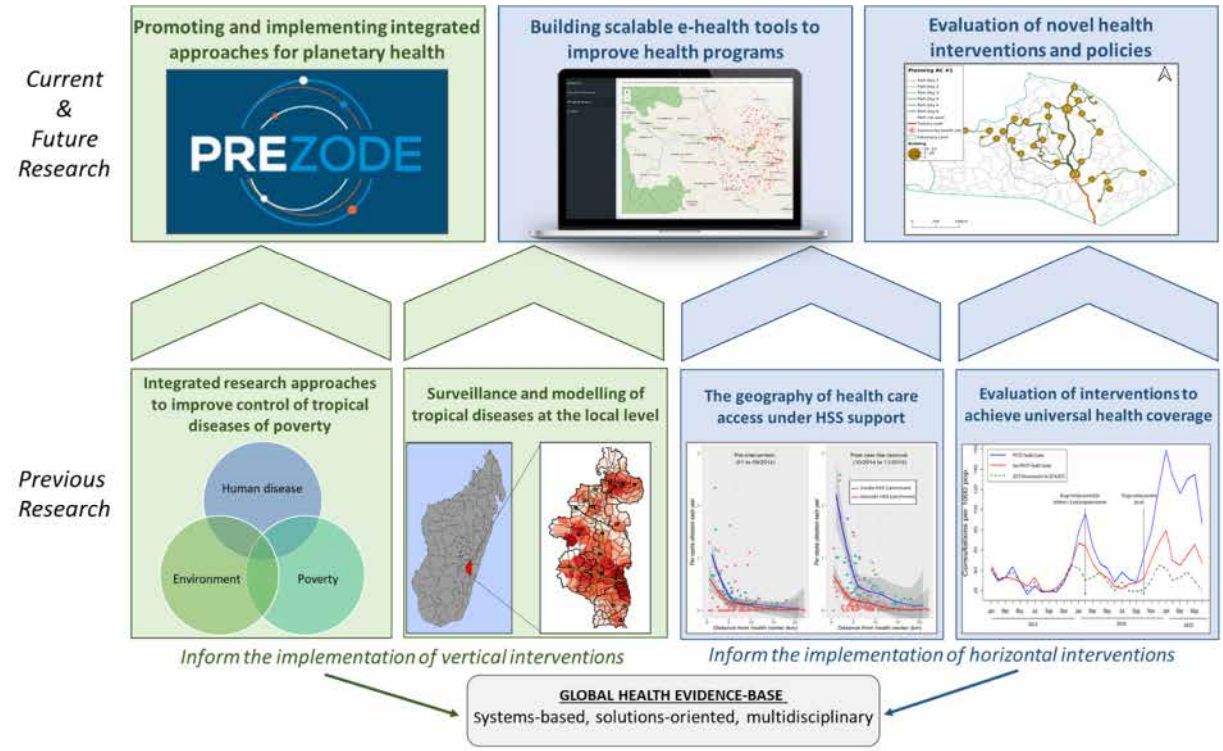

Figure 5. Représentation schématique de l'évolution de mon agenda scientifique. Elle montre mes trois principaux axes de recherche actuelle et future, ainsi que le lien avec les axes de recherche que j'ai développé au cours de ces 10 dernières années.

Développement d'outils e-santé pour améliorer les programmes de santé

Tout d'abord, les approches qui combinent l'information sur les systèmes de santé, la télédétection et la modélisation des maladies infectieuses éclairent de plus en plus la planification nationale ou régionale pour un meilleur contrôle des maladies [127], mais leur application au niveau local, où les efforts d'intervention ont effectivement lieu, reste largement inexplorée [128]. Les travaux antérieurs que j'ai effectués à Ifanadiana m'ont permis de reconnaître cette lacune et de poser les bases pour commencer à résoudre ce problème grâce à une étude pilote sur le paludisme en collaboration avec Pivot. L'objectif du projet *« SMALLER: Surveillance and control of malaria at the local level using e-health platforms »* financé par l'ANR et dont je suis investigateur principal, est de développer des modèles statistiques et mathématiques de transmission du paludisme qui informent les principales caractéristiques de la mise en œuvre du programme, aidant à adapter les stratégies de surveillance et de contrôle au niveau communautaire. Pour cela, nous couplons, au niveau d'un district sanitaire, une surveillance épidémiologique précise des cas de paludisme, des informations satellitaires à haute résolution et des données socio-économiques, afin d'acquérir une bonne compréhension de la dynamique locale du paludisme. En tirant parti de l'intervention RSS-CSU de Pivot et des systèmes de collecte de données en place à Ifanadiana, nous pilotons des outils d'aide à la décision innovants et fiables en matière de lutte contre le paludisme qui peuvent être validés localement et étendus à l'échelle mondiale. Les objectifs spécifiques de ce projet sont les suivants : 1) estimer le fardeau non observé du paludisme au niveau communautaire pour améliorer la surveillance; 2) intégrer des prévisions communautaires de la transmission du paludisme dans les flux de travail existants des agents communautaires dans le district d'Ifanadiana afin d'améliorer la mise en œuvre du programme; 3) mettre en œuvre des stratégies de lutte supplémentaires qui minimisent la transmission du paludisme, éclairées par des simulations de modèles de transmission.

Deuxièmement, pour optimiser les interventions locales de lutte contre le paludisme ciblant les populations enclavées et améliorer leur accès aux diagnostics et aux traitements du paludisme, une compréhension très précise de la géographie locale est nécessaire pour identifier les populations ayant une faible accessibilité géographique aux établissements de santé, planifier des missions sur le terrain et optimiser les itinéraires des agents de santé communautaires s'ils font des soins proactifs, et des équipes mobiles lors des campagnes (sensibilisation, distribution des moustiquaires, etc.). Notre travail pilote à Ifanadiana sur l'accès géographique aux soins, où nous avons combiné la cartographie de précision avec de nouvelles méthodes de modélisation géographique et le développement d'outils e-santé [121], a attiré l'attention d'organisations internationales telles que la President Malaria Initiative (PMI) de l'USAID, qui sont intéressées à étendre ces méthodes à d'autres parties de Madagascar dans le but d'informer la mise en œuvre d'interventions « dernier kilomètre » pour le paludisme. L'objectif du projet *« Malaria remote populations (MRP): scaling tools for fine-scale geographic accessibility modelling in South Eastern Madagascar »* financé par l'USAID-PMI et dont je suis l'investigateur principal, est d'étendre les travaux pilotés en Ifanadiana à cinq autres districts sanitaires de la région afin de développer des estimations très précises de l'accessibilité géographique aux soins. Comme précédemment, nous utiliserons une approche participative sur OpenStreetMap pour cartographier tous les sentiers, zones résidentielles et ménages dans les cinq districts afin de mesurer avec précision la distance aux établissements de santé pour chaque ménage de la zone d'étude. Nous obtiendrons des estimations de temps de trajet correspondantes, paramétrées avec des travaux de terrain et des analyses de télédétection à partir d'images satellites à haute résolution. Enfin, nous intégrerons les résultats dans une plateforme e-santé à l'usage des acteurs de santé locaux, régionaux et nationaux.

Évaluation de nouvelles interventions et politiques de santé

Tout d'abord, compte tenu du succès des interventions de prise en charge communautaire des maladies infantiles visant à améliorer l'accès aux soins et à réduire la mortalité, l'expansion à tous les âges de la prise en charge communautaire du paludisme (mCCM en anglais) peut éliminer certains des obstacles à la recherche précoce de soins, y compris la distance géographique et le manque de temps et de ressources pour visiter l'établissement de santé le plus proche, mais l'efficacité de ces efforts n'est pas claire. L'objectif du projet *« Évaluation de l'efficacité de la prise en charge communautaire des cas de paludisme (mCCM) pour tous les âges dans le district de Farafangana, Madagascar »*, financé par l'USAID-PMI et mis en œuvre en étroite collaboration avec le Ministère de la Santé et l'ONG Inter Aide, est d'évaluer si l'extension du mCCM à tous les âges augmente la proportion de personnes de tous âges qui sont testées pour le paludisme. La conception de ce projet pilote, pour lequel je suis co-investigateur principal, est un essai randomisé en grappes avec deux bras (intervention et contrôle) se déroulant dans la circonscription de 30 établissements de santé (15 par bras) comprenant environ 500 agents communautaires. Dans les deux bras, le système de santé communautaire est renforcé par des formations, des sensibilisations, des supervisions de routine et un soutien au système de gestion d'intrants. Les objectifs spécifiques de ce projet sont d'évaluer 1) si l'extension de la mCCM à tous les âges augmente la proportion de membres du ménage atteints de fièvre qui ont demandé des soins et, s'ils ont été testés positifs pour le paludisme, ont reçu un traitement avec un antipaludéen approprié, 2) si l'extension de la mCCM à tous les âges réduit la prévalence du paludisme chez les enfants de moins de 15 ans, 3) si l'élargissement de la mCCM à tous les âges affecte la proportion d'enfants de moins de 5 ans atteints d'une maladie qui cherchent à obtenir des soins pour une pneumonie et une diarrhée, 4) l'acceptabilité de l'extension à tous les âges de la mCCM, par les membres de la communauté, les agents communautaires et les professionnels des centres de santé, et 5) les coûts et le rapport coût-efficacité de l'extension de la mCCM à tous les âges. Afin d'évaluer l'efficacité de l'intervention, une enquête transversale auprès des ménages avec un échantillon de 1 680 ménages (840 par bras) est réalisée avant l'intervention et 24 mois plus tard. De plus, des enquêtes qualitatives et des données du système de santé sont recueillies. L'extension du mCCCM à tous les âges faisant partie du Plan stratégique contre le paludisme à Madagascar 2018-2022, l'étude est mise en place en tant que projet pilote dans un district endémique avant une mise à l'échelle nationale par le Ministère de la Santé qui sera soutenue par l'USAID-PMI et le Fonds mondial si les résultats sont encourageants.

Deuxièmement, je continuerai à élaborer progressivement un programme de recherche multidisciplinaire autour du RSS et la CSU qui éclaire le partenariat entre le Ministère de la Santé et l'ONG Pivot localement à Ifanadiana, fournit des leçons pour le gouvernement de Madagascar à l'échelle nationale, et génère des preuves scientifiques en santé mondiale sur le RSS, les politiques de CSU et les interventions de contrôle des maladies. Je dirigerai un ensemble de projets de recherche à Ifanadiana autour de trois sujets principaux: *i) l'impact au niveau de la population du RSS et de la CSU:* combinant les informations de la cohorte IHOPE avec les données du système de santé pour évaluer l'impact du RSS-CSU, avec une intervention qui s'étend géographiquement, évolue au niveau programmatique et s'adapte aux preuves produites par mon équipe de recherche. Compte tenu de la période plus longue, dans les analyses futures, j'évaluerai s'il y a des changements linéaires ou non linéaires dans les indicateurs de couverture des soins de santé, ainsi que l'impact de l'épidémie de COVID-19 sur les comportements de recherche de soins de santé; *ii) équité géographique dans l'accès aux soins :* je continuerai à développer de nouvelles recherches en géographie de la santé pour évaluer comment une bonne compréhension de la géographie locale peut influencer la prestation de soins de

santé à tous les niveaux du système de santé dans le district d'Ifanadiana (santé communautaire, soins primaires, hôpital). Par exemple, nous adaptons des algorithmes « traveling salesman » (tels que ceux utilisés par les entreprises de livraison à domicile) pour caractériser les itinéraires optimaux pour les soins proactifs afin de couvrir leur population et informer les besoins programmatiques en ressources humaines en fonction de la géographie; *iii) l'analyse des systèmes de santé, l'éco-épidémiologie et la surveillance :* combinant des informations environnementales (par exemple, la télédétection, la surveillance vectorielle), des informations de santé et socio-économiques sur la population, avec des modèles de transmission de maladies pour comprendre et prédire les dynamiques locales des maladies à Ifanadiana (au-delà du paludisme) et pour les intégrer dans des outils pour les agents de santé qui pourraient améliorer leurs activités.

Promotion et mise en œuvre des approches intégrées pour la santé planétaire

Il est maintenant reconnu que la santé des humains, des animaux et de l'environnement sont liés et que des cadres mondiaux d'étude et d'action (par exemple, « Une seule santé », « éco-santé » ou « santé planétaire ») sont nécessaires pour prévenir ou atténuer ces émergences. L'Initiative mondiale *« Preventing Zoonotic Disease Emergence (PREZODE) »* vise à promouvoir ce type d'approches globales dans la recherche opérationnelle afin de prévenir de futures pandémies. Je contribuerai à développer à Madagascar au cours des prochaines années l'un des premiers projets pilotes de l'initiative PREZODE financé par l'AFD dans cinq pays prioritaires. L'objectif du projet pilote de Madagascar (pour lequel je serai co-investigateur principal) sera de développer et de renforcer les capacités de surveillance des zoonoses prioritaires, telles que la fièvre du Rift et d'autres maladies à transmission vectorielle, ainsi que celles d'agents pathogènes provenant de la faune sauvage (par exemple, le hanta virus et le coronavirus), entre autres. Le projet, qui sera largement mis en œuvre dans le district d'Ifanadiana grâce au partenariat solide et aux connaissances que nous avons dans ce district, comprendra trois piliers principaux: (i) des activités de recherche permettant une meilleure compréhension, prédiction et gestion des facteurs de risque d'émergence zoonotique, (ii) la co-construction d'écosystèmes résilients aux risques zoonotiques avec les acteurs locaux, et (iii) la mise en œuvre de stratégies de surveillance et de détection précoce adaptées aux contextes épidémiologiques et aux pratiques et perceptions des acteurs locaux. En bref, nous combinerons des études épidémiologiques avec des collectes sur le terrain pour identifier les agents pathogènes en circulation, les personnes à risque, l'exposition communautaire et les risques d'exposition. Cela permettra de sensibiliser la communauté à ces risques, et d'induire des changements dans les pratiques pour les réduire. Enfin, nous augmenterons la capacité des systèmes de surveillance déjà en place en intégrant la surveillance de la santé humaine, animale et environnementale au niveau communautaire afin de détecter rapidement les événements anormaux qui pourraient entraîner l'émergence de maladies. La portée opérationnelle du projet pilote à Madagascar signifie que le projet sera mis en œuvre grâce à une collaboration entre des institutions de recherche, des organisations non gouvernementales et des agences gouvernementales.

8. References

1. Sachs J. Macroeconomics and Health: Investing in Health for Economic Development. Report of the Commission on Macroeconomics and Health. Geneva, Switzerland; 2001.

2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095–128. doi:10.1016/S0140-6736(12)61728-0.

3. Diamond J. Guns, germs, and steel: the fates of human societies. New York: W. W. Norton and Company; 1997.

4. Hibbs D a, Olsson O. Geography, biogeography, and why some countries are rich and others are poor. Proc Natl Acad Sci U S A. 2004;101:3715–20. doi:10.1073/pnas.0305531101.

5. Bonds MH, Dobson AP, Keenan DC. Disease ecology, biodiversity, and the latitudinal gradient in income. PLoS Biol. 2012;10:e1001456. doi:10.1371/journal.pbio.1001456.

6. Guernier V, Hochberg ME, Guégan J-F. Ecology drives the worldwide distribution of human diseases. PLoS Biol. 2004;2:e141. doi:10.1371/journal.pbio.0020141.

7. Dunn RR, Davies TJ, Harris NC, Gavin MC. Global drivers of human pathogen richness and prevalence. Proc Biol Sci. 2010;277:2587–95. doi:10.1098/rspb.2010.0340.

8. Gallup JL, Sachs JD, Mellinger A. Geography and economic development. Int Reg Sci Rev. 1999;:179–232.

9. Bloom DE, Sachs J. Geography , Demography , and Economic Growth in Africa. Brookings Pap Econ Act. 1998;:207–295.

10. McMichael AJ, Friel S, Nyong A, Corvalan C. Global environmental change and health: impacts, inequalities, and the health sector. BMJ. 2008;336:191–4. doi:10.1136/bmj.39392.473727.AD.

11. Costello A, Abbas M, Allen A, Ball S, Bell S, Bellamy R, et al. Managing the health effects of climate change. Lancet. 2009;373:1693–733. doi:10.1016/S0140-6736(09)60935-1.

12. United Nations General Assembly. Transforming our world: the 2030 Agenda for Sustainable Development. 2015.

13. Garchitorena A, Sokolow SH, Roche B, Ngonghala CN, Jocque M, Lund A, et al. Disease ecology, health and the environment: A framework to account for ecological and socio-economic drivers in the control of neglected tropical diseases. Philos Trans R Soc B Biol Sci. 2017;372.

14. Bonds MH, Keenan DC, Rohani P, Sachs JD. Poverty trap formed by the ecology of infectious diseases. Proc Biol Sci. 2010;277:1185–92. doi:10.1098/rspb.2009.1778.

15. Ngonghala CN, Pluciński MM, Murray MB, Farmer PE, Barrett CB, Keenan DC, et al. Poverty, disease, and the ecology of complex systems. PLoS Biol. 2014;12:e1001827. doi:10.1371/journal.pbio.1001827.

16. World Health Organization. Sustaining the drive to overcome the global impact of neglected tropical diseases. Geneva, Switzerland; 2013.

17. World Health Organization. Working to overcome the global impact of neglected tropical diseases First WHO report on neglected tropical diseases. Geneva, Switzerland; 2010.

18. Hotez PJ, Kamath A. Neglected tropical diseases in sub-saharan Africa: review of their prevalence, distribution, and disease burden. PLoS Negl Trop Dis. 2009;3:e412. doi:10.1371/journal.pntd.0000412.

19. Mathers CD, Ezzati M, Lopez AD. Measuring the burden of neglected tropical diseases: the global burden of disease framework. PLoS Negl Trop Dis. 2007;1:e114. doi:10.1371/journal.pntd.0000114.

20. Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Ehrlich Sachs S, Sachs JD. Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. PLoS Med. 2006;3:e102. doi:10.1371/journal.pmed.0030102.

21. Fenwick a. The global burden of neglected tropical diseases. Public Health. 2012;126:233–6. doi:10.1016/j.puhe.2011.11.015.

22. Johnson PDR, Stinear T, Small PLC, Pluschke G, Merritt RW, Portaels F, et al. Buruli ulcer (M. ulcerans infection): new insights, new hope for disease control. PLoS Med. 2005;2:e108. doi:10.1371/journal.pmed.0020108.

23. Grietens KP, Boock AU, Peeters H, Hausmann-Muela S, Toomer E, Ribera JM. "It is me who endures but my family that suffers": social isolation as a consequence of the household cost burden of Buruli ulcer free of charge hospital treatment. PLoS Negl Trop Dis. 2008;2:e321. doi:10.1371/journal.pntd.0000321.

24. Stienstra Y, van Roest MHG, van Wezel MJ, Wiersma IC, Hospers IC, Dijkstra PU, et al. Factors associated with functional limitations and subsequent employment or schooling in Buruli ulcer patients. Trop Med Int Heal. 2005;10:1251–7. doi:10.1111/j.1365-3156.2005.01519.x.

25. Merritt RW, Walker ED, Small PLC, Wallace JR, Johnson PDR, Benbow ME, et al. Ecology and transmission of Buruli ulcer disease: a systematic review. PLoS Negl Trop Dis. 2010;4:e911. doi:10.1371/journal.pntd.0000911.

26. Meyers WM, Shelly WM, Connor DH. Human Mycobacterium ulcerans infections developing at sites of trauma to skin. Am J Trop Med Hyg. 1974;23:919–23.

27. Marsollier L, Robert R, Aubry J, Andre J Saint, Kouakou H, Legras P, et al. Aquatic Insects as a Vector for Mycobacterium ulcerans. Appl Environ Microbiol. 2002;68:4623–8.

28. Portaels F, Elsen P, Guimaraes-Peres a, Fonteyne P a, Meyers WM. Insects in the transmission of Mycobacterium ulcerans infection. Lancet. 1999;353:986. doi:10.1016/S0140-6736(98)05177-0.

29. Garchitorena A, Roche B, Kamgang R, Ossomba J, Babonneau J, Landier J, et al. Mycobacterium ulcerans Ecological Dynamics and Its Association with Freshwater Ecosystems and Aquatic Communities: Results from a 12-Month Environmental Survey in Cameroon. PLoS Negl Trop Dis. 2014;8:e2879. doi:10.1371/journal.pntd.0002879.

30. Garchitorena A, Guégan J-F, Léger L, Eyangoh S, Marsollier L, Roche B. Mycobacterium ulcerans dynamics in aquatic ecosystems are driven by a complex interplay of abiotic and biotic factors. Elife. 2015;4:e07616.

31. García-Peña GE, Garchitorena A, Carolan K, Canard E, Prieur-Richard A-HH, Suzán G, et al. Niche-based host extinction increases prevalence of an environmentally acquired pathogen. Oikos. 2016;125 January:1508–15. doi:10.1111/oik.02700.

32. Carolan K, Garchitorena A, García-Peña GE, Morris A, Landier J, Fontanet A, et al. Topography and Land Cover of Watersheds Predicts the Distribution of the Environmental Pathogen Mycobacterium ulcerans in Aquatic Insects. PLoS Negl Trop Dis. 2014;8.

33. Carolan K, Ebong SM a SM, Garchitorena A, Landier J, Sanhueza D, Texier G, et al. Ecological niche modelling of Hemipteran insects in Cameroon; the paradox of a vector-borne transmission for Mycobacterium ulcerans, the causative agent of Buruli ulcer. Int J Health Geogr. 2014;13:44. doi:10.1186/1476-072X-13-44.

34. Garchitorena A, Ngonghala CN, Texier G, Landier J, Eyangoh S, Bonds MH, et al. Environmental transmission of Mycobacterium ulcerans drives dynamics of Buruli ulcer in endemic regions of Cameroon. Nat Sci Reports. 2015;5 November:18055. doi:10.1038/srep18055.

35. Garchitorena A, Ngonghala CN, Guegan J-F, Texier G, Bellanger M, Bonds M, et al. Economic inequality caused by feedbacks between poverty and the dynamics of a rare tropical disease: The case of buruli ulcer in sub-Saharan Africa. Proc R Soc B Biol Sci. 2015;282.

36. Landier J, de Magny GC, Garchitorena A, Guégan J-F, Gaudart J, Marsollier L, et al. Seasonal patterns of buruli ulcer incidence, central Africa, 2002–2012. Emerg Infect Dis. 2015;21.

37. Eisenberg MC, Robertson SL, Tien JH. Identifiability and estimation of multiple transmission pathways in cholera and waterborne disease. J Theor Biol. 2013;324:84–102. doi:10.1016/j.jtbi.2012.12.021.

38. Codeço CT. Endemic and epidemic dynamics of cholera: the role of the aquatic reservoir. BMC Infect Dis. 2001;1:1.

39. Tien JH, Earn DJD. Multiple transmission pathways and disease dynamics in a waterborne pathogen model. Bull Math Biol. 2010;72:1506–33.

40. Miguel E, Kremer M. Worms : Identifying Impacts on Education and Health in the Presence of Treatment Externalities. Econometrica. 2004;72:159–217.

41. Sachs J, Malaney P. The economic and social burden of malaria. Nature. 2002;415:680–5. doi:10.1038/415680a.

42. Nokes C, Grantham-McGregor SM, Sawyer AW, Cooper ES, Bundy DA. Parasitic helminth infection and cognitive function in school children. Proc Biol Sci. 1992;247:77–81. doi:10.1098/rspb.1992.0011.

43. Rist CL, Garchitorena A, Ngonghala CN, Gillespie TR, Bonds MH. The Burden of Livestock Parasites on the Poor. Trends in Parasitology. 2015;31:527–30.

44. Rist CL, Ngonghala CN, Garchitorena A, Brook CE, Ramananjato R, Miller AC, et al. Modeling the burden of poultry disease on the rural poor in Madagascar. One Heal. 2015;1.

45. Abbafati C, Abbas KM, Abbasi-Kangevari M, Abd-Allah F, Abdelalim A, Abdollahi M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396:1204–22.

46. Metcalf CJE, Walter KS, Wesolowski A, Buckee CO, Shevliakova E, Tatem AJ, et al. Identifying climate drivers of infectious disease dynamics: recent advances and challenges ahead. Proceedings Biol Sci. 2017;284. doi:10.1098/rspb.2017.0901.

47. Rogers DJ, Randolph SE, Snow RW, Hay SI. Satellite imagery in the study and forecast of malaria. Nature. 2002;415:710–5. doi:10.1038/415710a.

48. Ikeda T, Behera SK, Morioka Y, Minakawa N, Hashizume M, Tsuzuki A, et al. Seasonally lagged effects of climatic factors on malaria incidence in South Africa. Sci Rep. 2017;7:1–9.

49. Kang SY, Battle KE, Gibson HS, Ratsimbasoa A, Randrianarivelojosia M, Ramboarina S, et al. Spatio-temporal mapping of Madagascar's Malaria Indicator Survey results to assess Plasmodium falciparum endemicity trends between 2011 and 2016. BMC Med. 2018;16:1–15.

50. Diboulo E, Sié A, Diadier DA, Voules DAK, Yé Y, Vounatsou P. Bayesian variable selection in modelling geographical heterogeneity in malaria transmission from sparse data: An application to Nouna Health and Demographic Surveillance System (HDSS) data, Burkina Faso. Parasites and Vectors. 2015;8:1–14.

51. Nguyen G, Kulikoff R, Casey DC, Bhatt S, Rozier J, Bisanzio D, et al. Mapping Plasmodium falciparum Mortality in Africa between 1990 and 2015 . N Engl J Med. 2016;375:2435–45.

52. Hamilton M, Mahiane G, Werst E, Sanders R, Briët O, Smith T, et al. Spectrum-Malaria: A user-friendly projection tool for health impact assessment and strategic planning by malaria control programmes in sub-Saharan Africa. Malar J. 2017;16:1–15.

53. Bennett A, Bisanzio D, Yukich JO, Mappin B, Fergus CA, Lynch M, et al. Population coverage of artemisinin-based combination treatment in children younger than 5 years with fever and Plasmodium falciparum infection in Africa, 2003–2015: a modelling study using data from national surveys. Lancet Glob Heal. 2017;5:e418–27. doi:10.1016/S2214-109X(17)30076-1.

54. Singh RBK, Hales S, De Wet N, Raj R, Hearnden M, Weinstein P. The influence of climate variation and change on diarrheal disease in the Pacific Islands. Environ Health Perspect. 2001;109:155–9.

55. Colston JM, Zaitchik B, Kang G, Peñataro Yori P, Ahmed T, Lima A, et al. Use of earth observation-derived hydrometeorological variables to model and predict rotavirus infection (MAL-ED): a multisite cohort study. Lancet Planet Heal. 2019;3:e248–58.

56. Herrera D, Ellis A, Fisher B, Golden CD, Johnson K, Mulligan M, et al. Upstream watershed condition predicts rural children's health across 35 developing countries. Nat Commun. 2017;8. doi:10.1038/s41467-017-00775-2.

57. Fewtrell L, Kaufmann RB, Kay D, Enanoria W, Haller L, Colford JM. Water, sanitation, and hygiene

interventions to reduce diarrhoea in less developed countries: A systematic review and meta-analysis. Lancet Infect Dis. 2005;5:42–52.

58. Wilkes G, Edge TA, Gannon VPJ, Jokinen C, Lyautey E, Neumann NF, et al. Associations among pathogenic bacteria, parasites, and environmental and land use factors in multiple mixed-use watersheds. Water Res. 2011;45:5807–25. doi:10.1016/j.watres.2011.06.021.

59. Evans M V., Bonds MH, Cordier LF, Drake JM, Ihantamalala F, Haruna J, et al. Socio-demographic, not environmental, risk factors explain fine-scale spatial patterns of diarrhoeal disease in Ifanadiana, rural Madagascar. Proceedings Biol Sci. 2021;288:20202501.

60. Singh N, Bharti PK, Kumre NS. Active v. passive surveillance for malaria in remote tribal belt of Central India: Implications for malaria elimination. Pathog Glob Health. 2016;110:178–84. doi:10.1080/20477724.2016.1223920.

61. Olotu A, Fegan G, Williams TN, Sasi P, Ogada E, Bauni E, et al. Defining Clinical Malaria: The Specificity and Incidence of Endpoints from Active and Passive Surveillance of Children in Rural Kenya. PLoS One. 2010;5:1–8.

62. Tiono AB, Kangoye DT, Rehman AM, Kargougou DG, Kaboré Y, Diarra A, et al. Malaria incidence in children in South-West Burkina Faso: Comparison of active and passive case detection methods. PLoS One. 2014;9:1–11.

63. Zhou G, Afrane YA, Malla S, Githeko AK, Yan G. Active case surveillance, passive case surveillance and asymptomatic malaria parasite screening illustrate different Age distribution, spatial clustering and seasonality in western Kenya. Malar J. 2015;14:1–8.

64. Feikin DR, Nguyen LM, Adazu K, Ombok M, Audi A, Slutsker L, et al. The impact of distance of residence from a peripheral health facility on pediatric health utilisation in rural western Kenya. Trop Med Int Heal. 2009;14:54–61.

65. McLaren, Zoe, Ardington, Cally, Leibbrandt M. Distance decay and persistent health care inequality in South Africa. BioMed Cent. 2014;:1–9.

66. Gething PW, Johnson FA, Frempong-Ainguah F, Nyarko P, Baschieri A, Aboagye P, et al. Geographical access to care at birth in Ghana: A barrier to safe motherhood. BMC Public Health. 2012;12:1. doi:10.1186/1471-2458-12-991.

67. Noor AM, Zurovac D, Hay SI, Ochola SA, Snow RW. Defining equity in physical access to clinical services using geographical information systems as part of malaria planning and monitoring in Kenya. Trop Med Int Heal. 2003;8:917–26.

68. Stock R. Distance and utilization of health facilities in rural Nigeria. Soc Sci Med. 2012;17:563–70.

69. World Health Organization. Global technical strategy for malaria 2016-2030. 2015. doi:ISBN: 978 92 4 156499 1.

70. Hyde E, Bonds MH, Ihantamalala FA, Miller AC, Cordier LF, Razafinjato B, et al. Estimating the local spatio-temporal distribution of malaria from routine health information systems in areas of low health care access and reporting. Int J Health Geogr. 2021;20:1–17. doi:10.1186/s12942-021-00262-4.

71. WHO. Global programme to eliminate lymphatic filariasis: progress report, 2015. Wkly Epidemiol Rec. 2016;39:441–60. http://www.who.int/lymphatic_filariasis/resources/who_wer9139/en/.

72. Global Program to Eliminate Lymphatic Filariasis. Training in monitoring and Epidemiological Assessment of Mass Drug Administration for Eliminating Lymphatic Filariasis: Learners' guide. Geneva, Switzerland; 2013.

73. Service de Lutte contre les Maladies Epidémiques et Négligées. Plan directeur de lutte contre les maladies tropicales negligees (MTN) 2016-2020. Antananarivo, Madagascar; 2016.

74. Garchitorena A, Raza-Fanomezanjanahary EM, Mioramalala SA, Chesnais C, Ratsimbasoa CA, Ramarosata H, et al. Towards elimination of lymphatic filariasis in southeastern Madagascar: Successes and challenges for interrupting transmission. PLoS Negl Trop Dis. 2018;12:e0006780. doi:10.1371/journal.pntd.0006780.

75. World Health Organization. Investing to overcome the global impact of neglected tropical diseases: Third

WHO report on neglected tropical diseases. Geneva, Switzerland; 2015. http://apps.who.int/iris/bitstream/10665/152781/1/9789241564861_eng.pdf.

76. Atun RA, Bennett S, Duran A. When do vertical (stand-alone) programmes have a place in health systems? WHO Eur Minist Conf Heal Syst. 2008;:1–28.

77. Stenberg K, Hanssen O, Edejer TTT, Bertram M, Brindley C, Meshreky A, et al. Financing transformative health systems towards achievement of the health Sustainable Development Goals: a model for projected resource needs in 67 low-income and middle-income countries. Lancet Glob Heal. 2017;5:e875–87.

78. Giedion U, Alfonso EA, Díaz Y. The Impact of Universal Coverage Schemes in the Developing World: A Review of the Existing Evidence. Washington DC; 2013.

79. Hatt L, Johns B, Connor C, Meline M, Kukla M, Moat K. Impact of Health Systems Strengthening on Health. Bethesda, MD: Health Finance and Governance Project, Abt Associates Inc; 2015.

80. Garchitorena A, Murray MB, Hedt-Gauthier B, Farmer PE, Bonds MH. Reducing the knowledge gap in global health delivery: contributions and limitations of randomized controlled trials. In: Bedecarrats F, Guerin I, Roubaud F, editors. Randomized Control Trials in the Field of Development. Oxford: Oxford University Press; 2020. p. 425.

81. World Health Organization and the International Bank for Reconstruction and Development / The World Bank. Tracking Universal Health Coverage: 2017 Global Monitoring Report. 2017. doi:ISBN 978-92-4-151355-5.

82. Kruk ME, Yamey G, Angell SY, Beith A, Cotlear D, Guanais F, et al. Transforming Global Health by Improving the Science of Scale-Up. PLOS Biol. 2016;14:e1002360. doi:10.1371/journal.pbio.1002360.

83. Brummitt CD, Huremović K, Pin P, Bonds MH, Vega-Redondo F. Contagious disruptions and complexity traps in economic development. Nat Hum Behav. 2017;1:665–72. doi:10.1038/s41562-017-0190-6.

84. Cameron DB, Mishra A, Brown AN. The growth of impact evaluation for international development: how much have we learned? J Dev Eff. 2016;8:1–21. doi:10.1080/19439342.2015.1034156.

85. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, et al. Evidence-based interventions for improvement of maternal and child nutrition: What can be done and at what cost? Lancet. 2013;382:452–77.

86. Whidden C, Kayentao K, Liu JX, Lee S, Keita Y, Diakité D, et al. Improving Community Health Worker performance by using a personalised feedback dashboard for supervision: a randomised controlled trial. J Glob Health. 2018;8:020418. doi:10.7189/jogh.08.020418.

87. Kelaher M, Ng L, Knight K, Rahadi A. Equity in global health research in the new millennium: Trends in first-authorship for randomized controlled trials among low and middle-income country researchers 1990-2013. Int J Epidemiol. 2016;45:2174–83.

88. Frieden TR. Evidence for Health Decision Making - Beyond Randomized, Controlled Trials. N Engl J Med. 2017;377:465–75. doi:10.1056/NEJMra1614394.

89. Deaton A, Cartwright N. Understanding and misunderstanding randomized controlled trials. Soc Sci Med. 2018;210 October 2017:2–21. doi:10.1016/j.socscimed.2017.12.005.

90. World Health Organization. Declaration of Astana. Geneva, Switzerland; 2018.

91. Miller AC, Garchitorena A, Rabeza V, Randriamanambintsoa M, Razanadrakato H-TR, Cordier L, et al. Cohort Profile: Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation (IHOPE). Int J Epidemiol. 2018;0:1–7.

92. Miller AC, Ramananjato RH, Garchitorena A, Rabeza VR, Gikic D, Cripps A, et al. Baseline population health conditions ahead of a health system strengthening program in rural Madagascar. Glob Health Action. 2017;10:1329961. doi:10.1080/16549716.2017.1329961.

93. Garchitorena A, Miller AC, Cordier LF, Ramananjato R, Rabeza VR, Murray M, et al. In Madagascar, use of health care services increased when fees were removed: Lessons for universal health coverage. Health Aff. 2017;36:1443–51.

94. Garchitorena A, Miller AC, Cordier LF, Rabeza VR, Randriamanambintsoa M, Razanadrakato H-TR, et al. Early changes in intervention coverage and mortality rates following the implementation of an integrated health system intervention in Madagascar. BMJ Glob Heal. 2018;3:e000762.

95. Garchitorena A, Miller AC, Cordier LF, Razanadrakato TR, Randriamanambintsoa M, Randriamihaja M, et al. District-level health system strengthening for universal health coverage : evidence from a longitudinal cohort study in rural Madagascar , 2014- 2018. BMJ Glob Heal. 2020;5:e003647.

96. Kruk ME, Gage AD, Joseph NT, Danaei G, García-Saisó S, Salomon JA. Mortality due to low-quality health systems in the universal health coverage era: a systematic analysis of amenable deaths in 137 countries. Lancet. 2018;6736. doi:10.1016/S0140-6736(18)31668-4.

97. Kruk ME, Larson E, Twum-Danso NAY. Time for a quality revolution in global health. Lancet Glob Heal. 2016;4:e594–6.

98. Kruk ME, Gage AD, Arsenault C, Jordan K, Leslie HH, Roder-DeWan S, et al. The Lancet Global Health Commission High-quality health systems in the Sustainable Development Goals era: time for a revolution. 2018;:1–57. doi:10.1016/S2214-109X(18)30386-3.

99. Adam T, Hsu J, De Savigny D, Lavis JN, Rottingen JA, Bennett S. Evaluating health systems strengthening interventions in low-income and middle-income countries: Are we asking the right questions? Health Policy Plan. 2012;27 SUPPL. 4.

100. Benova L, Tunçalp Ö, Moran AC, Campbell OMR. Not just a number: examining coverage and content of antenatal care in low-income and middle-income countries. BMJ Glob Heal. 2018;3:e000779. doi:10.1136/bmjgh-2018-000779.

101. Kruk ME, Gage AD, Mbaruku GM, Leslie HH. Content of Care in 15,000 Sick Child Consultations in Nine Lower-Income Countries. Health Serv Res. 2018.

102. Ezran C, Bonds MH, Miller AC, Cordier LF, Haruna J, Mwanawabenea D, et al. Assessing trends in the content of maternal and child care following a health system strengthening initiative in rural Madagascar : A longitudinal cohort study. PLoS Med. 2019;16:1–23.

103. Rajaonarifara E, Bonds MH, Miller AC, Ihantamalala FA, Cordier L, Razafinjato B, et al. Impact of health system strengthening on delivery strategies to improve child immunisation coverage and inequalities in rural Madagascar. BMJ Glob Heal. 2022;7:1–13.

104. Dhillon RS, Bonds MH, Fraden M, Ndahiro D, Ruxin J. The impact of reducing financial barriers on utilisation of a primary health care facility in Rwanda. Glob Public Health. 2011;2007 Table 1:1–16. doi:10.1080/17441692.2011.593536.

105. Langlois É V., Karp I, De Dieu Serme J, Bicaba A. Effect of a policy to reduce user fees on the rate of skilled birth attendance across socioeconomic strata in Burkina Faso. Health Policy Plan. 2016;31:462–71.

106. Zombré D, De Allegri M, Ridde V. Immediate and sustained effects of user fee exemption on healthcare utilization among children under five in Burkina Faso: A controlled interrupted time-series analysis. Soc Sci Med. 2017;179:27–35.

107. Lagarde M, Palmer N. The impact of user fees on access to health services in low- and middle-income countries (Review). Cochrane Database Syst Rev. 2011.

108. Johri M, Ridde V, Heinmüller R, Haddad S. Estimation of maternal and child mortality one year after user-fee elimination: an impact evaluation and modelling study in Burkina Faso. Bull World Health Organ. 2014;92 September 2013:706–15. doi:10.2471/BLT.13.130609.

109. Bates MA, Glennerster R, Gumede K, Duflo E. The Price is Wrong. F Actions Sci Reports. 2012; Special Issue 4. http://factsreports.revues.org/1554. Accessed 19 Jan 2016.

110. Ciapponi A, Lewin S, Ca H, Opiyo N, Pantoja T, Paulsen E, et al. Delivery arrangements for health systems in low-income countries : an overview of systematic reviews (Review). Cochrane Database Syst Rev. 2017;1:1–182.

111. Oo WH, Gold L, Moore K, Agius PA, Fowkes FJI. The impact of community-delivered models of malaria control and elimination: A systematic review. Malar J. 2019;18:1–16. doi:10.1186/s12936-019-2900-1.

112. Makanga PT, Schuurman N, Von Dadelszen P, Firoz T. A scoping review of geographic information systems in maternal health. Int J Gynecol Obstet. 2016;134:13–7. doi:10.1016/j.ijgo.2015.11.022.

113. Alegana VA, Wright JA, Pentrina U, Noor AM, Snow RW, Atkinson PM. Spatial modelling of healthcare utilisation for treatment of fever in Namibia. Int J Health Geogr. 2012;11:1–13. http://eds.b.ebscohost.com.ezproxy.lib.usf.edu/eds/pdfviewer/pdfviewer?sid=cdcaab37-c5a1-48bb-a716-5b4726638305%40sessionmgr198&vid=7&hid=119.

114. Bailey PE, Keyes EB, Parker C, Abdullah M, Kebede H, Freedman L. Using a GIS to model interventions to strengthen the emergency referral system for maternal and newborn health in Ethiopia. Int J Gynecol Obstet. 2011;115:300–9.

115. Makanga PT, Schuurman N, Sacoor C, Boene HE, Vilanculo F, Vidler M, et al. Seasonal variation in geographical access to maternal health services in regions of southern Mozambique. Int J Health Geogr. 2017;16:1. doi:10.1186/s12942-016-0074-4.

116. Ray N, Ebener S. AccessMod 3.0: computing geographic coverage and accessibility to health care services using anisotropic movement of patients. Int J Health Geogr. 2008;7:63.

117. Black M, Ebener S, Aguilar PN, Vidaurre M, Morjani Z El. Using GIS to Measure Physical Accessibility to Health Care. World Heal Organ. 2004;3–4:1–22.

118. Ouma PO, Maina J, Thuranira PN, Macharia PM, Alegana VA, English M, et al. Access to emergency hospital care provided by the public sector in sub-Saharan Africa in 2015: a geocoded inventory and spatial analysis. Lancet Glob Heal. 2018;6:e342–50. doi:10.1016/S2214-109X(17)30488-6.

119. Juran S, Broer PN, Klug SJ, Snow RC, Okiro EA, Ouma PO, et al. Geospatial mapping of access to timely essential surgery in sub-Saharan Africa. BMJ Glob Heal. 2018;3:e000875. doi:10.1136/bmjgh-2018-000875.

120. Weiss DJ, Nelson A, Vargas-Ruiz CA, Gligorić K, Bavadekar S, Gabrilovich E, et al. Global maps of travel time to healthcare facilities. Nat Med. 2020.

121. Ihantamalala FA, Herbreteau V, Revillion C, Randriamihaja M, Commins J, Andreambeloson T, et al. Improving geographical accessibility modeling for operational use by local health actors. Int J Health Geogr. 2020;:1–15.

122. Ihantamalala FA, Bonds MH, Randriamihaja M, Rakotonirina L, Herbreteau V, Révillion C, et al. Geographic barriers to establishing a successful hospital referral system in rural Madagascar. BMJ Glob Heal. 2021;6.

123. Wigley AS, Tejedor-Garavito N, Alegana V, Carioli A, Ruktanonchai CW, Pezzulo C, et al. Measuring the availability and geographical accessibility of maternal health services across sub-Saharan Africa. BMC Med. 2020;18:1–10.

124. Meara JG, Leather AJM, Hagander L, Alkire BC, Alonso N, Ameh EA, et al. Global Surgery 2030: Evidence and solutions for achieving health, welfare, and economic development. Lancet. 2015;386:569–624.

125. Garchitorena A, Ihantamalala FA, Révillion C, Cordier LF, Randriamihaja M, Razafinjato B, et al. Geographic barriers to achieving universal health coverage: evidence from rural Madagascar. Health Policy Plan. 2021;00:1–12. https://academic.oup.com/heapol/advance-article/doi/10.1093/heapol/czab087/6332582.

126. Emergency care systems for universal health coverage: ensuring timely care for the acutely ill and injured. Seventy-second World Health Assembly. 2019. https://apps.who.int/iris/handle/10665/329158.

127. Girond F, Randrianasolo L, Randriamampionona L, Rakotomanana F, Randrianarivelojosia M, Ratsitorahina M, et al. Analysing trends and forecasting malaria epidemics in Madagascar using a sentinel surveillance network: a web-based application. Malar J. 2017;16:72. doi:10.1186/s12936-017-1728-9.

128. World Health Organization. World malaria report 2016. 2016.

129. Yucel RM. Multiple imputation inference for multivariate multilevel continuous data with ignorable non-

response. Philos Trans R Soc A Math Phys Eng Sci. 2008;366:2389–403.

130. Griffin JT, Hollingsworth TD, Okell LC, Churcher TS, White M, Hinsley W, et al. Reducing Plasmodium falciparum malaria transmission in Africa: A model-based evaluation of intervention strategies. PLoS Med. 2010;7.

131. Bousema T, Griffin JT, Sauerwein RW, Smith DL, Churcher TS, Takken W, et al. Hitting hotspots: Spatial targeting of malaria for control and elimination. PLoS Med. 2012;9:1–7.

9. Annexe 1. Main publications

- **Garchitorena A**, Guégan J-F, Léger L, Eyangoh S, Marsollier L, Roche B. Mycobacterium ulcerans dynamics in aquatic ecosystems are driven by a complex interplay of abiotic and biotic factors. *Elife*. 2015;4:e07616.
- **Garchitorena A**, Sokolow S, Roche B, Ngonghala CN, Jocque M, Lund A, Barry M, Mordecai EA, Daily GC, Jones JH, Andrews JR, Bendavid E, Luby SP, LaBeaud A, Seetah K, Guégan J, Bonds M, De Leo G. Disease Ecology, Health and Environment: a framework to account for ecological and socio-economic drivers in the control of neglected tropical diseases. *Philos Trans R Soc B Biol Sci*. **2017**;372(1722).
- Ezran C, Bonds MH, Miller AC, Cordier LF, Haruna J, Mwanawabenea D, Randriamanambintsoa M, Razanadrakato R, Ouenzar MA, Murray M, **Garchitorena A**. Assessing trends in the content of maternal and child care following a health system strengthening initiative in rural Madagascar : A longitudinal cohort study. *PLoS Med*. **2019**;16(8):1–23.
- **Garchitorena A**, Ihantamalala FA, Révillion C, Cordier LF, Randriamihaja M, Razafinjato B, Rafenoarivamalala FH, Finnegan KE, Andrianirinarison JC, Rakotonirina J, Herbreteau V, Bonds MH. Geographic barriers to achieving universal health coverage: evidence from rural Madagascar. *Health Policy Plan*. **2021**;00:1–12.
- Rajaonarifara E, Bonds MH, Miller AC, Ihantamalala FA, Cordier L, Razafinjato B, Rafenoarimalala FH, Finnegan KE, Rakotonanahary RJL, Cowley G, Ratsimbazafy B, Razafimamonjy F, Randriamanambintsoa M, Raza-Fanomezanjanahary EM, Randrianambinina A, Metcalf CJ, Roche B, **Garchitorena A**. Impact of health system strengthening on delivery strategies to improve child immunisation coverage and inequalities in rural Madagascar. *BMJ Glob Heal*. **2022**;7(1):1–13.

eLIFE elifesciences.org

RESEARCH ARTICLE

Mycobacterium ulcerans dynamics in aquatic ecosystems are driven by a complex interplay of abiotic and biotic factors

Andrés Garchitorena[1,2]*, Jean-François Guégan[1,2,6], Lucas Léger[1], Sara Eyangoh[3], Laurent Marsollier[4], Benjamin Roche[5]

[1]Maladies Infectieuses et Vecteurs: Ecologie, Génétique, Evolution et Contrôle (UMR CNRS/IRD/UM 5290), Montpellier, France; [2]Ecole des Hautes Etudes en Santé Publique, Rennes, France; [3]Laboratoire de Mycobactériologie, Centre Pasteur du Cameroun, Réseau International des Instituts Pasteur, Yaoundé, Cameroon; [4]Institut National de la Recherche Médicale U892 (INSERM) et CNRS U6299, équipe 7, Université et CHU d'Angers, Angers, France; [5]International Center for Mathematical and Computational Modelling of Complex Systems (UMI IRD/UPMC UMMISCO), Bondy Cedex, France; [6]International programme Future Earth, ecoHEALTH Initiative, Ottawa, Canada

Abstract Host–parasite interactions are often embedded within complex host communities and can be influenced by a variety of environmental factors, such as seasonal variations in climate or abiotic conditions in water and soil, which confounds our understanding of the main drivers of many multi-host pathogens. Here, we take advantage of a combination of large environmental data sets on *Mycobacterium ulcerans* (*MU*), an environmentally persistent microorganism associated to freshwater ecosystems and present in a large variety of aquatic hosts, to characterize abiotic and biotic factors driving the dynamics of this pathogen in two regions of Cameroon. We find that *MU* dynamics are largely driven by seasonal climatic factors and certain physico-chemical conditions in stagnant and slow-flowing ecosystems, with an important role of *pH* as limiting factor. Furthermore, water conditions can modify the effect of abundance and diversity of aquatic organisms on *MU* dynamics, which suggests a different contribution of two *MU* transmission routes for aquatic hosts (trophic vs environmental transmission) depending on local abiotic factors.
DOI: 10.7554/eLife.07616.001

***For correspondence:** andres.garchitorena@gmail.com

Competing interests: The authors declare that no competing interests exist.

Funding: See page 14

Received: 24 March 2015
Accepted: 25 June 2015
Published: 28 July 2015

Reviewing editor: Quarraisha Abdool Karim, University of KwaZulu Natal, South Africa

Introduction

Despite increased understanding of infectious disease ecology and dynamics, recent decades have seen an upsurge in the emergence and re-emergence of multiple infectious diseases (***Jones et al., 2008***). Most emerging pathogens are zoonotic and have a very broad range of hosts (***Woolhouse et al., 2001***; ***Woolhouse and Gowtage-Sequeria, 2005***), and as a result, host–parasite interactions are often embedded within complex host communities (***Plowright et al., 2008***; ***Roche et al., 2013b***). Biotic interactions between hosts in the community may play an important role on disease transmission, either promoting or diluting the overall prevalence of the pathogen (***LoGiudice et al., 2003***; ***Keesing et al., 2010***; ***Johnson et al., 2013***; ***Roche et al., 2013a***). In addition, the effect of seasonal variations in climate on abiotic conditions in water and soil can influence the composition of host communities and in turn have an impact on the ecological dynamics of the pathogens

eLife digest *Mycobacterium ulcerans* is a slow-growing bacterium that causes a rare tropical disease in humans called Buruli ulcer. The infection affects the skin and underlying tissues, initially causing small painless lesions that can develop into large open sores or ulcers that are responsible for significant handicap in rural areas of sub-Saharan Africa.

Disease outbreaks generally occur in close association with stagnant and slow-flowing aquatic ecosystems, mostly after floods or other large environmental disturbances. It is believed that contact with water sources that contain the bacteria causes infection in humans, but the specific mode of transmission remains a mystery. By defining the factors that influence the bacteria's presence in the environment, public health officials could develop initiatives that would reduce an individual's risk of infection when conditions support a *M. ulcerans* outbreak.

To identify the environmental conditions that affect the prevalence of *M. ulcerans* in two regions of Cameroon where Buruli ulcer is present, Garchitorena et al. have now analyzed a large amount of ecological data about the bacteria using cutting-edge statistical techniques. This revealed that the amount of *M. ulcerans* varies following seasonal changes in climate, at least in the region dominated by tropical rainforest. In this region, the bacteria are also generally present in waters that are more alkaline and contain fewer animals, especially from certain species that could prevent the infection spreading to other aquatic hosts. In the other region, dominated by a savannah landscape, the bacteria are most abundant in stagnant or slowly moving waters that have optimal physical and chemical conditions and contain many diverse species of potential animal hosts. The discovery of contrasting results for the two regions suggests that there are at least two ways that *M. ulcerans* can persist in the environment and infect the aquatic animals. The prevailing method—through environmental transmission or through interactions between hosts—depends on the properties of the water.

Many other infectious diseases are caused by pathogens that, like *M. ulcerans*, infect many different hosts and persist in the environment for long periods. Future research following methods like those used by Garchitorena et al. would help to reveal whether these pathogens are affected by environmental factors in similar ways to *M. ulcerans*.

DOI: 10.7554/eLife.07616.002

(***Ostfeld et al., 2008***). Because of the intertwined nature of biotic and abiotic drivers, disentangling their respective contribution to pathogen dynamics and transmission through complex and different-scale processes remains a challenge (***Plowright et al., 2008***). Nonetheless, identifying the underlying ecological mechanisms driving the emergence and persistence of diseases is essential to reduce disease risk in human populations (***Roche and Guégan, 2011***).

An illustrative example is the case of *Mycobacterium ulcerans* (*MU*), an environmentally persistent microorganism associated to freshwater ecosystems in tropical countries and present in a large variety of aquatic hosts (***Benbow et al., 2008***; ***Marion et al., 2010***; ***Garchitorena et al., 2014***). From a public health perspective, *MU* is the agent responsible for Buruli ulcer (BU), a devastating skin disease with great health and socio-economic consequences in tropical and subtropical countries (***WHO, 2008***). Emergence, distribution, and risk factors for BU in many parts of the world are associated with stagnant and slow-flowing ecosystems (***Brou et al., 2008***; ***Wagner et al., 2008***; ***Jacobsen and Padgett, 2010***; ***Marion et al., 2011***). The environmental factors that favour *MU* persistence and transmission within these ecosystems are still poorly understood but the environmental and multi-host nature of the pathogen suggests that its environmental dynamics can be the result of a complex interplay between environmental factors and biotic interactions (***Garchitorena et al., 2014***; ***Morris et al., 2014***).

MU is broadly present across taxa in aquatic communities over space and time (***Benbow et al., 2008***; ***Marion et al., 2010***; ***Garchitorena et al., 2014***), suggesting that a multiplicity of hosts can play a role in *MU* persistence in the environment. Biotic interactions between hosts are thought to be a pathogen transmission route between organisms (***Merritt et al., 2010***), with *MU* being integrated in the aquatic community from the environment thanks to filter feeder, herbivorous, and scavenger organisms and then transmitted across the community through predation (***Marsollier et al., 2002***, ***2007a***, ***2007b***; ***Mosi et al., 2008***). As a result, community-level factors such as biodiversity or

abundance of aquatic organisms could drive the environmental load of *MU* through amplification or dilution effects, as demonstrated for other pathogens (**Ezenwa et al., 2006**; **Suzán et al., 2009**; **Keesing et al., 2010**; **Johnson et al., 2013**). Furthermore, some keystone species could play an overwhelming role in the transmission and overall *MU* prevalence in host communities (**Roche et al., 2013a**).

Some specific water conditions, physical or chemical, could also favour *MU* environmental persistence and dynamics in aquatic ecosystems. *MU* seems to grow better under laboratory conditions with low oxygen, high temperature, and mildly acidic *pH* (**Portaels and Pattyn, 1982**; **Palomino and Portaels, 1998**; **Palomino et al., 1998**; **Dega et al., 2000**; **Marsollier et al., 2004**). Genomic studies show that *MU* is sensitive to UV light (**Stinear et al., 2007**; **Doig et al., 2012**) so turbid or protected environments could promote *MU* persistence. Many of these conditions are generally met in swamps and other stagnant and slow-flowing ecosystems, and therefore, if optimal abiotic conditions are met, *MU* could grow and persist in these ecosystems as free-living stages in the water and infect aquatic organisms directly, without the need for a trophic transmission to take place. Besides, numerous abiotic factors within aquatic ecosystems can influence host community structures and assemblages (**Eric Benbow et al., 2013**; **Garchitorena et al., 2014**), since aquatic invertebrate and vertebrate taxa have different ranges of optimal water conditions (**Dickens and Graham, 2002**). This could represent an indirect influence of abiotic conditions on *MU* transmission within aquatic communities.

A direct transmission of *MU* driven mostly by abiotic factors and a trophic transmission driven by biological interactions are not two mutually exclusive routes but rather could complement each other to allow persistence of *MU* under a wide range of environments. Identifying the contribution of such transmission routes requires a deep understanding of the dynamics of *MU* within aquatic communities through space and time. A recent characterization of *MU* dynamics with unprecedented detail in two BU endemic areas with very distinct environmental conditions (**Garchitorena et al., 2014**) offers the variability needed to address this question. Indeed, in Bankim, a region located in a transition zone between forest and savannah, swamps had remarkably higher *MU* positivity, as initially expected, whereas in Akonolinga, where rainforest is the prevailing landscape, all ecosystems had similar *MU* positivity. These regional differences suggested that savannah swamps had unique favourable conditions for *MU* that were not found elsewhere, but *MU* was still able to persist in unfavourable environments. Furthermore, temporal fluctuations in *MU* presence in Akonolinga suggested a potential role of seasonal climatic events as drivers of *MU* dynamics.

Relying on this work, the aim of this paper is to study for the first time the contribution of ecological factors, both biotic and abiotic, to the dynamics of *MU* in the aquatic environment. More specifically, we attempt to identify a set of abiotic conditions that could be optimal for *MU* growth and allow direct transmission to aquatic organisms, likely in stagnant waters and, in the absence of these, explore which biotic factors could still allow *MU* to persist, potentially through trophic transmission. Insights into the ecological mechanisms allowing for *MU* growth and persistence over space and time, while accounting for the potential impact of seasonal climatic events, may have profound implications for understanding BU risk to human populations.

To address these questions, we model *MU* positivity in 32 aquatic communities over time with generalized linear mixed models (GLMMs), including all relevant seasonal, abiotic, and biotic factors as fixed effects. We use cutting-edge multi-model selection procedures and information theory to identify and quantify the most important predictors of *MU* dynamics, using a genetic algorithm to screen multiple models from all potential combinations of explanatory variables and making inference from a set of weighted best-performing models. In addition, we back the results of this novel approach, which deals with the uncertainty associated with model selection, by comparing them to those obtained by classical model selection procedures. We then discuss the implications of disentangling biotic and abiotic factors for host/parasite interactions and the importance of rigorously analysing the underlying drivers of pathogen dynamics mediated through complex and different-scale processes.

Results

By simultaneously accounting for multiple seasonal, abiotic, and biotic factors, our results show the complex interplay that drives *MU* environmental dynamics. In a previous step to the statistical modelling of *MU* positivity, we performed principal component analysis (PCA) of the most relevant

physico-chemical characteristics in the water, as a means to explore common patterns in the ecosystems and to include these PCs as alternative abiotic predictors in the model. The ecosystems sampled and followed up in both Akonolinga and Bankim regions consistently revealed common physico-chemical patterns depending on water flow (**Table 1**). The first PC, explaining about 50% of variation in aquatic ecosystems in both regions, showed a positive correlation between water flow, dissolved oxygen, and *pH*, while temperature was inversely correlated. Furthermore, the inverse correlation between temperature and water flow held in the second PC, and the positive correlation between water flow and oxygen was also present in the third PC. Using multi-model selection for our GLMMs, a combination of seasonal factors, water conditions (abiotic factors), and community-level characteristics (biotic factors) remained as important predictors of *MU* positivity in the final set of best models for Akonolinga (**Table 2**) and Bankim (**Table 3**). Among all possible models tested, 39 were selected for estimation of model average estimates in Akonolinga and 100 in Bankim, since these models were similarly performing according to their Akaike Information Criterion (AIC) scores (see the methodology section). Although all factors were included together as part of the full model, the results explained below are divided in groups of factors for clarity. Furthermore, comparison of multi-model inference results with those obtained by classical model selection procedures can be found in Appendix 1, section 1.

Effect of seasonality on *M. ulcerans*

Seasonality was investigated by including *sine* and *cosine* functions as independent predictors of *MU* positivity. The presence of *MU* in aquatic ecosystems in Akonolinga was associated to seasonal variations with a single annual cycle as revealed by the positive effect of the *sine* function on *MU* (b = 0.36; 95% confidence interval (CI) [0.04, 0.67], w_i = 1) and the presence of this variable in all best models (**Table 2**). On the contrary, the seasonal effect in Bankim was not apparent, where only 4 months of collection were available, and none of the *sine* and *cosine* functions were important in the final models for this region (**Table 3**).

Effect of abiotic conditions on *M. ulcerans*

Among all abiotic conditions, included in the models both as individual physico-chemical variables or through their combined effect as PCs, *pH* had a significant positive effect in all best models in Akonolinga (**Table 2**), either through the effect of component 2 that is directly correlated with *pH* (b = 0.49; 95% CI [0.21, 0.76], w_i = 0.56) or as individual variable in the remaining models (b = 7.15; 95% CI [2.56, 11.73], w_i = 0.44). In Bankim, however, the most important abiotic factor was water flow (**Table 3**). Lentic water bodies (low water flow) had significantly lower *MU* positivity than stagnant waters (b = −1.80; 95%CI [−3.04, −0.56], w_i = 1), and lotic water bodies (high water flow) had the lowest *MU* positivity (b = −3.63; 95% CI [−5.35, −1.91], w_i = 1). It is important to note that water flow in most environments was directly correlated with *pH*, and thus each region provides contrasting results for this abiotic factor.

Table 1. Description of environments defined by principal components analysis (PCA) of physico-chemical parameters

	Akonolinga				Bankim			
	PC1	PC2	PC3	PC4	PC1	PC2	PC3	PC4
Variance explained	0.47	0.31	0.14	0.09	0.59	0.22	0.13	0.07
Loadings								
pH	−0.33	0.7	−0.47	0.41	−0.51	0.51	−0.43	0.55
Dissolved oxygen	−0.6	0.31	0.31	−0.67	−0.57	0.33	0.11	−0.75
Water flow	−0.59	−0.32	0.46	0.59	−0.51	−0.29	0.72	0.36
Temperature	0.43	0.55	0.69	0.19	0.4	0.74	0.53	0.1

Separate PCA was performed for Akonolinga and Bankim, and only the most potentially relevant parameters were included.

DOI: 10.7554/eLife.07616.003

Table 2. Results from multi-model selection for Akonolinga (12 months of sampling)

Variable	Avg. effect (*b*)	Uncond. SE	Lower CL	Upper CL	Relative importance (w_i)	Nb. models
(Intercept)	2.71	4.04	−5.21	10.63	1.00	39
Seasonality						
Sine (2pi*Month/12)	**0.36**	**0.16**	**0.04**	**0.67**	**1.00**	**39**
Sine (2pi*Month/4)	–	–	–	–	–	–
Cosine (2pi*Month/12)	–	–	–	–	–	–
Cosine (2pi*Month/4)	–	–	–	–	–	–
Physico-chemical parameters						
pH	**7.15**	**2.34**	**2.56**	**11.73**	**0.44**	**17**
Flow	–	–	–	–	–	–
Temperature	–	–	–	–	–	–
Dissolved oxygen	–	–	–	–	–	–
Conductivity	–	–	–	–	–	–
Iron	–	–	–	–	–	–
Physico-chemical parameters (PCA)						
PC2	**0.49**	**0.14**	**0.21**	**0.76**	**0.56**	**22**
PC1	–	–	–	–	–	–
PC3	–	–	–	–	–	–
Community						
Abundance	**−0.71**	**0.18**	**−1.07**	**−0.35**	**1.00**	**39**
Shannon	–	–	–	–	–	–
Aquatic taxa (%)						
Gastropoda	**−0.58**	**0.17**	**−0.92**	**−0.24**	**1.00**	**39**
Oligochaeta (Presence)	0.40	0.28	−0.14	0.95	0.92	36
Odonata	0.08	0.15	−0.21	0.37	0.87	34
Hydracarina	0.19	0.29	−0.39	0.76	0.85	33
Trichoptera	−0.01	0.16	−0.31	0.30	0.67	26
Decapoda (Presence)	**−1.10**	**0.38**	**−1.84**	**−0.35**	**0.59**	**23**
Hirudinea (Presence)	0.48	0.26	−0.02	0.99	0.59	23
Coleoptera	0.24	0.20	−0.15	0.63	0.54	21
Hemiptera	**−0.54**	**0.21**	**−0.94**	**−0.13**	**0.54**	**21**
Anura	**−0.41**	**0.16**	**−0.73**	**−0.09**	**0.41**	**16**
Ephemeroptera	0.07	0.15	−0.21	0.36	0.21	8
Diptera	−0.07	0.15	−0.38	0.23	0.10	4

Variables within each category are ordered by their relative importance. Variables with their 95% confidence interval (CI) with the same sign are represented in bold. Rare aquatic taxa are introduced in the model as Presence/Absence variables, while relative abundance is used for more abundant taxa.

DOI: 10.7554/eLife.07616.004

Effect of biotic interactions on *M. ulcerans*

The impact of aquatic communities on *MU* was studied through the effect of both individual aquatic taxa and community-level factors such as abundance and diversity. In Akonolinga, we found a negative association between total abundance and *MU* presence in all final models ($b = -0.71$; 95% CI [−1.07, −0.35], $w_i = 1$) and individual effects of several taxa. Individual taxa inversely correlated with *MU* were Gastropoda in all models ($b = -0.58$; 95% CI [−0.92, −0.24], $w_i = 1$) and Decapoda ($b = -1.10$; 95% CI [−1.84, −0.35], $w_i = 0.59$), Hemiptera ($b = -0.54$; 95% CI [−0.94, −0.13], $w_i = 0.54$), and Anura ($b = -0.41$, 95% CI [−0.73, −0.09], $w_i = 0.41$), with lower importance in the final models

Table 3. Results from multi-model selection for Bankim (4 months of sampling)

Variable	Avg. effect (*b*)	Uncond. SE	Lower CL	Upper CL	Relative importance (w_i)	Nb. Models
(Intercept)	**−13.98**	**4.13**	**−22.07**	**−5.89**	**1.00**	**100**
Seasonality						
Sine (2pi*Month/12)	–	–	–	–	–	–
Sine (2pi*Month/4)	–	–	–	–	–	–
Cosine (2pi*Month/12)	–	–	–	–	–	–
Cosine (2pi*Month/4)	–	–	–	–	–	–
Physico-chemical parameters						
Water flow (lentic)	**−1.80**	**0.63**	**−3.04**	**−0.56**	**1.00**	**100**
Water flow (lotic)	**−3.63**	**0.88**	**−5.35**	**−1.91**	**1.00**	**100**
pH	–	–	–	–	–	–
Temperature	–	–	–	–	–	–
Dissolved oxygen	–	–	–	–	–	–
Conductivity	–	–	–	–	–	–
Iron	–	–	–	–	–	–
Physico-chemical parameters (PCA)						
PC3	0.44	0.39	−0.33	1.21	0.07	7
PC2	0.34	0.41	−0.47	1.15	0.03	3
PC1	**0.67**	**0.33**	**0.03**	**1.32**	**0.01**	**1**
Community						
Abundance	0.86	0.47	−0.06	1.79	1.00	100
Shannon	**4.29**	**1.21**	**1.93**	**6.66**	**1.00**	**100**
Aquatic taxa (%)						
Gastropoda	−0.39	0.30	−0.97	0.18	0.90	90
Anura	−0.54	0.37	−1.26	0.19	0.89	89
Trichoptera	−0.05	0.64	−1.30	1.20	0.89	89
Odonata	−0.05	0.30	−0.63	0.53	0.87	87
Fish	−0.89	0.56	−1.98	0.20	0.86	86
Coleoptera	−0.04	0.35	−0.73	0.65	0.84	84
Diptera	0.70	0.49	−0.26	1.66	0.84	84
Hirudinea (Presence)	−0.41	0.43	−1.25	0.44	0.69	69
Hydracarina	**−1.42**	**0.55**	**−2.50**	**−0.33**	**0.58**	**58**
Decapoda (Presence)	1.76	1.23	−0.66	4.17	0.53	53
Hemiptera	−0.07	0.33	−0.72	0.57	0.22	22
Oligochaeta (Presence)	−0.02	0.48	−0.96	0.92	0.14	14
Ephemeroptera	**−0.84**	**0.25**	**−1.33**	**−0.35**	**0.13**	**13**

Variables within each category are ordered by their relative importance. Variables with their 95% CI with the same sign are represented in bold. Rare aquatic taxa are introduced in the model as Presence/Absence variables, while relative abundance is used for more abundant taxa. Results for lentic and lotic ecosystems represent the decrease in *MU* respective to stagnant ecosystems.

DOI: 10.7554/eLife.07616.005

(***Table 2***). Finally, the orders Oligochaeta, Odonata, and Hydracarina had a large importance in the final models (w_i > 0.80), but their effect on *MU* presence was not significant. Results for Bankim revealed a significant positive effect in all models for Shannon's diversity index (b = 4.29; 95% CI [1.93, 6.66], w_i = 1) and nearly significant for total abundance (b = 0.86; 95% CI [−0.06, 1.79], w_i = 1). In addition, most taxonomic orders appeared in the final models for this region, but their effect was unclear (***Table 3***). The estimates for taxonomic groups with a relative importance over 0.8

(Gastropoda, Anura, Trichoptera, Odonata, Fish, Coleoptera, and Diptera) had considerable uncertainty, with upper and lower CIs of opposite sign. The only two orders with a significant CI were Hydracarina (b = −1.42, 95% CI [−2.50, −0.33]) and Ephemeroptera (−0.84; 95% CI [−1.33, −0.35]), but their relative importance was relatively low (w_i = 0.58 and w_i = 0.13, respectively).

Discussion

Understanding how environmental factors influence host–pathogen interactions in complex natural systems, where multiple feedbacks between biotic and abiotic factors take place, is especially important in the context of multi-host and environmentally persistent pathogens. In this study, we identify abiotic and biotic drivers that may promote or block *MU* transmission in aquatic communities in two climatically distinct regions of Cameroon through a comprehensive multi-model selection procedure. In Akonolinga, we show that *MU* follows seasonal dynamics and is mainly present in waters with higher *pH* and within low abundance communities, notably those with low abundance of Gastropoda and other orders such as Decapoda, Hemiptera, or Anura. In Bankim, we show that *MU* is most prevalent in stagnant ecosystems and those with low water flow, with highly diverse (and abundant) communities.

A seasonal effect for *MU* presence in Akonolinga remains in our final models after accounting for abiotic and biotic parameters in the water bodies, which also vary seasonally. This suggests that seasonal fluctuations in *MU* presence might be directly related to climatic pressures (***Figure 1***). Indeed, while the seasonal effect is not directly linked to rainfall dynamics (Pearson's correlation test, p = 0.45), it is highly correlated with the 3-month mean rainfall accumulation in the region (Current month, plus two previous months; Pearson's correlation test, p < 0.01). As a result, we propose that the cumulative effect of rainfall over several months, increasing water levels in the environment either boosts *MU* growth or washes it off from other environmental matrices (mud, soil, plants) to aquatic ecosystems, as previously suggested from epidemiological evidence (***Morris et al., 2014***). Furthermore, given the slow growth of *MU* (***Palomino and Portaels, 1998***; ***Stinear et al., 2007***), the 2-month delay between the peaks in the dynamics of rainfall and those of the seasonal effect could

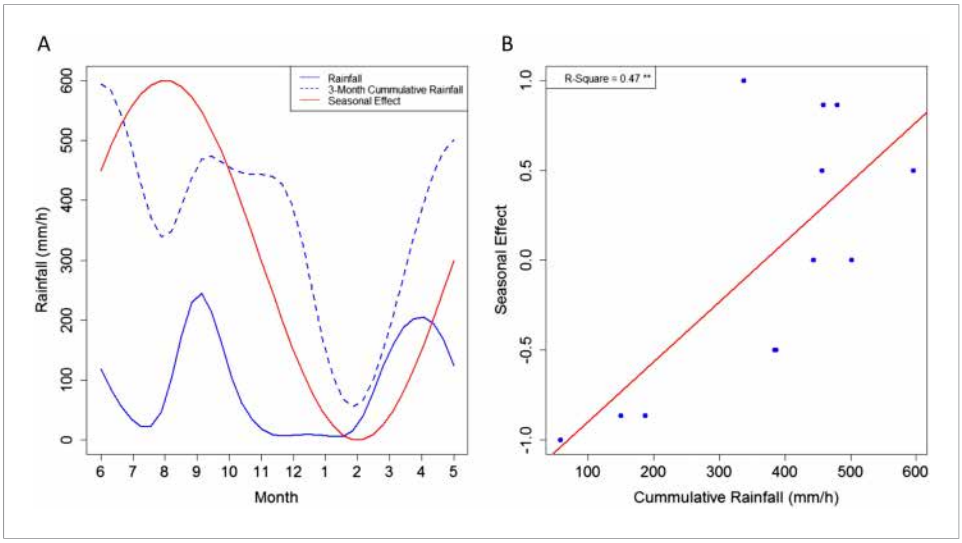

Figure 1. Link between the seasonal effect for *M. ulcerans* and the rainfall dynamics in Akonolinga. (**A**) Represents the monthly values for the seasonal effect (red), the mean rainfall for the period under study and the 3-month cumulative rainfall (blue). (**B**) Shows a clear linear relationship between the values of the seasonal effect and the 3-month cumulative rainfall. A graphical representation of the different seasonal effects tested can be found in ***Figure 1—figure supplement 1***.

DOI: 10.7554/eLife.07616.006

The following figure supplement is available for figure 1:

Figure supplement 1. Values for the different seasonal effects tested in the statistical models.

DOI: 10.7554/eLife.07616.007

represent the time that takes *MU* to grow and/or be transmitted through the aquatic community once the suitable habitats have been created. Unfortunately, the less frequent sampling in Bankim (only 4 months instead of 12) may have prevented to capture seasonal variations appropriately, explaining the lack of associations with *MU* in this region.

Our results for Bankim support the hypothesis that, under certain circumstances, conditions in stagnant and slow-flowing (lentic) bodies of water are favourable for *MU* presence. After controlling for all the other abiotic and biotic factors, sites with stagnant waters in this area have higher *MU* positivity than those with lentic waters (slow flow), and these have in turn higher positivity than sites with lotic waters (faster flow). PCA on physico-chemical parameters of these ecosystems provides some potential explanations (***Figure 2***). Sites with stagnant or lower water flows have higher temperatures (PC1 and PC2) and most have lower oxygen (PC1) and lower *pH* (PC1), all of which seem to promote *MU* growth in experimental studies (***Portaels and Pattyn, 1982***; ***Palomino and Portaels, 1998***;

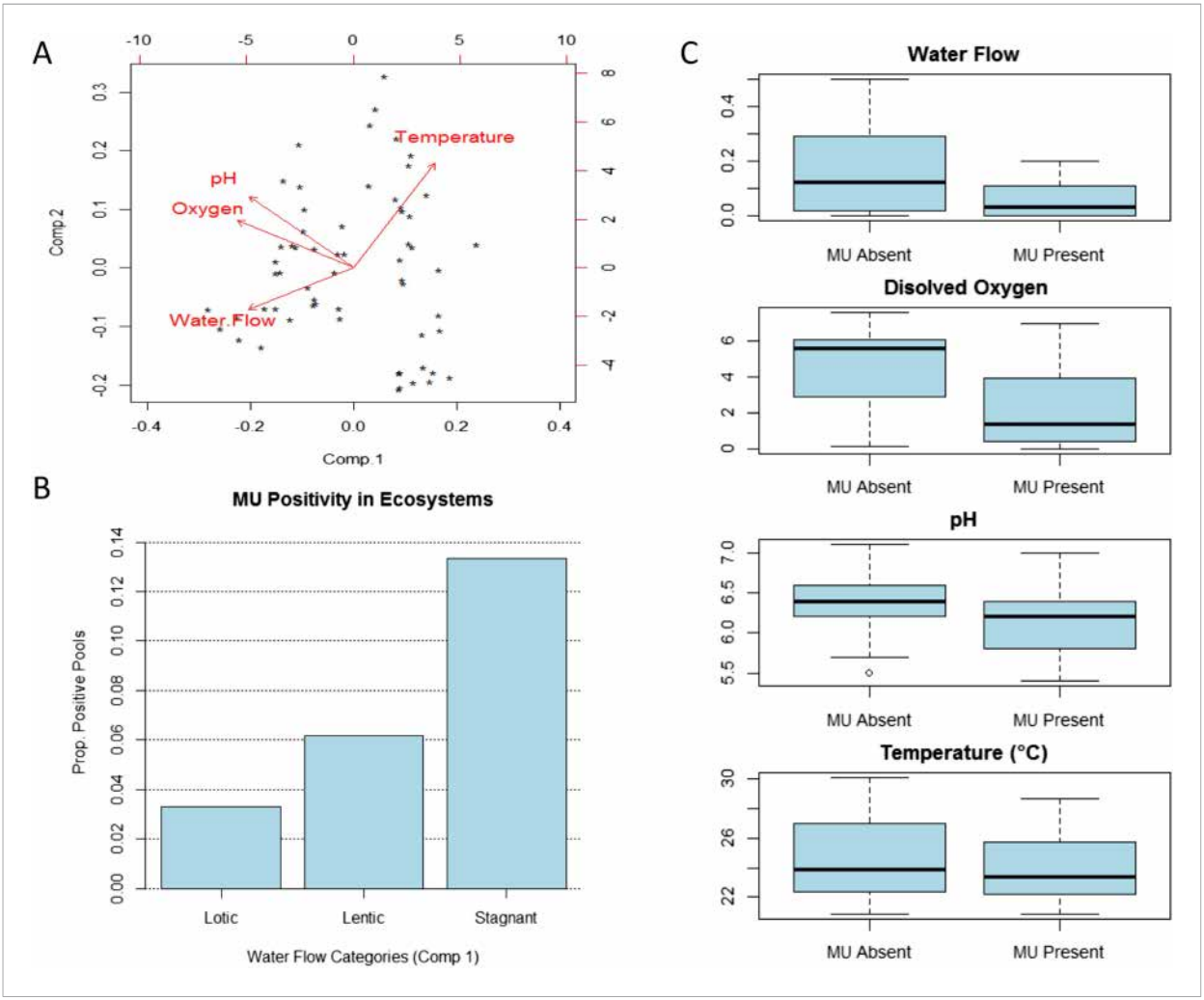

Figure 2. Impact of water flow on physico-chemical characteristics of the water and *M. ulcerans* prevalence in aquatic communities (Bankim). (**A**) Links between water conditions in the first two principal components obtained through principal component analysis (PCA). Comp.1, explaining more than 50% of the variation in physico-chemical conditions in Bankim, reveals that ecosystems with lower water flows have less dissolved oxygen, more acidic *pH*, and higher temperature. (**B**) *MU* positivity in each type of ecosystem as described by the first component of the PCA, which takes into account variations in all physico-chemical characteristics (each category has equal number of points and increasing values of Comp.1). Stagnant ecosystems in Bankim have higher *MU* positivity than lentic, and these have in turn higher *MU* positivity than lotic ecosystems. (**C**) Difference in values for the various water conditions in *MU* positive and *MU* negative sites in Bankim. As a result of the association of water flow with the other physico-chemical conditions, similar patterns for *MU* positivity can be observed for most abiotic conditions.

DOI: 10.7554/eLife.07616.008

Palomino et al., 1998; *Dega et al., 2000*; *Marsollier et al., 2004*). Indeed, a previous field study suggested that some water characteristics may be important for the presence of mycobacteria in water and biofilms throughout the year (*Hennigan et al., 2013*).

While stagnant waters with lower *pH* contribute significantly to *MU* presence in Bankim, the results for Akonolinga show a positive association between *pH* and *MU* in this region. Significantly lower *pH* values in Akonolinga than in Bankim (t-test, $p < 0.001$) may be behind the disparity between the model results for each region (*Figure 3*). Indeed, *pH* range for slow-growing mycobacteria has been estimated between 5.8 and 6.5 (*Portaels and Pattyn, 1982*), which corresponds to the lower range of *pH* in Bankim, associated with stagnant waters. Because in Akonolinga, this optimal range corresponds to the upper range of values, stagnant waters with intolerably low *pH* might not meet all the optimal conditions for *MU* growth, which would explain the lack of association with these ecosystems (*Garchitorena et al., 2014*). The role of *pH* on *MU* growth in combination with other

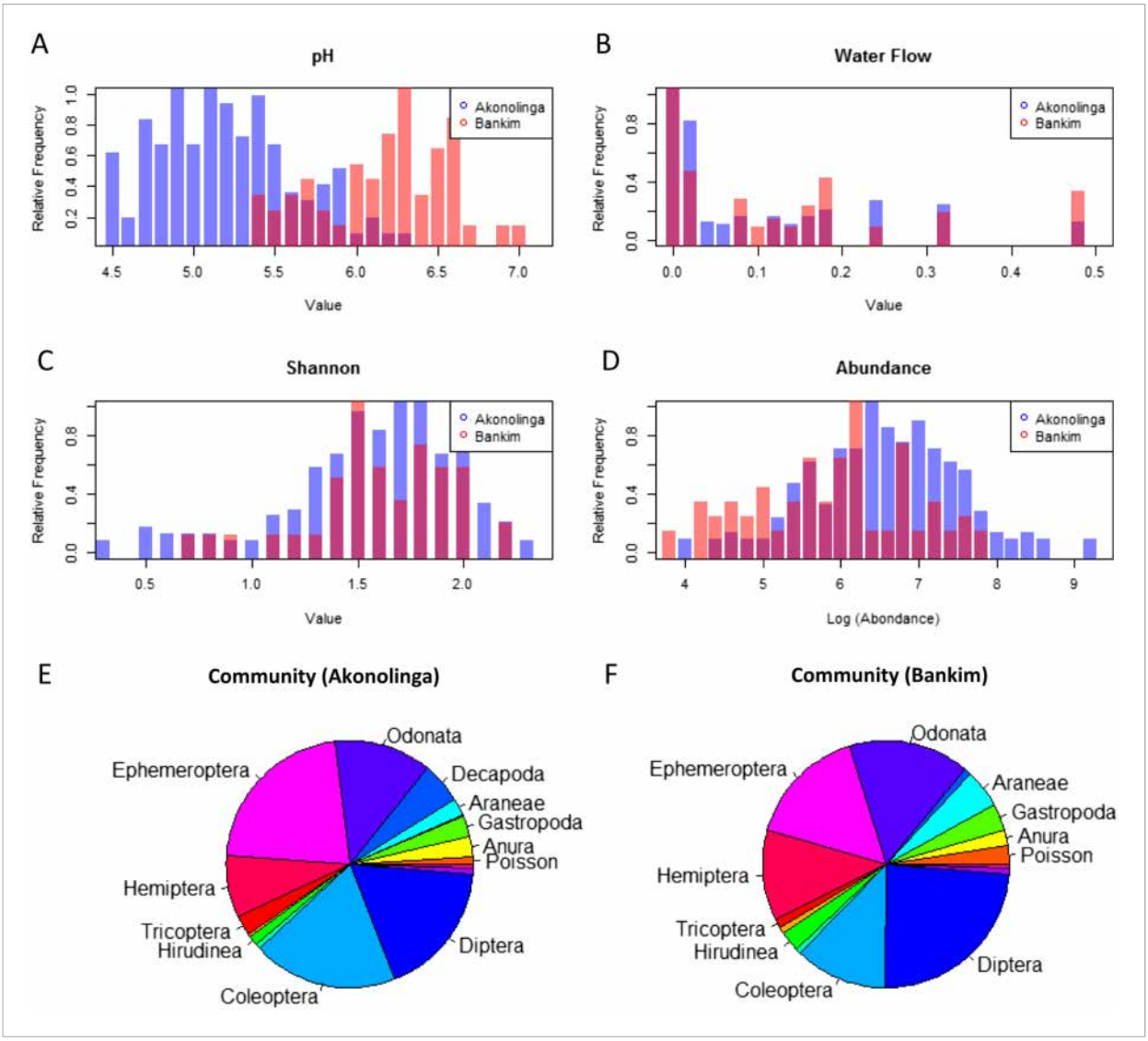

Figure 3. Distribution of relevant biotic and abiotic variables for Akonolinga and Bankim. For the construction of histograms (**A**–**D**), the relative frequency of the variable within each region is normalized by dividing each frequency by its maximum frequency. It can be noted that the distribution of *pH* is radically different for both regions, with much more acidic *pH* in aquatic environments from Akonolinga. For the community composition (**E** and **F**), the area an order has in the pie chart is proportional to the mean relative abundance of the order for all sites and months for each region. Only orders representing more than 1% of the overall community are labelled.

DOI: 10.7554/eLife.07616.009

abiotic conditions needs to be urgently assessed, since it might be an important limiting factor in the environment.

Biotic interactions seem to have an important effect on *MU* positivity in the local aquatic communities, especially in Akonolinga. Less abundant communities are associated with a reduction of *MU* in this region, and individual taxa have an independent effect on *MU*. Higher relative abundance of aquatic snails (Gastropoda), shrimps (Decapoda), water bugs (Hemiptera), and tadpoles (Anura) is associated with reduced *MU* prevalence in the aquatic community. The protective role of aquatic snails is supported by experimental infections, where *MU* has been unable to grow within these organisms (**Marsollier and Sévérin, 2004**), but this is not the case for Hemipteran water bugs, where *MU* can grow and even colonize their salivary glands after they have fed on infected prey (**Marsollier et al., 2002**, **2005**; **Mosi et al., 2008**). Even though water bugs can host *MU* and allow its growth, they are voracious predators of aquatic organisms, and therefore, an increase in water bugs in the community may result in a decrease of infected prey available to other predators such as Coleoptera or Odonata; this could result in an overall reduction in *MU* positivity. This is an example of how considering the full breadth of factors taking place in real ecological systems can provide unexpected insights on this type of host–pathogen interactions. Furthermore, differences in community composition may partly explain the different effects of biotic factors in the two regions (**Figure 3C–F**). Total abundance in aquatic communities was significantly higher in Akonolinga (Mann–Whitney test, $p < 0.001$), and the relative abundance of more than half of the taxa included in our model was significantly different between Akonolinga and Bankim (Appendix 1, section 2).

These different distributions of biotic and abiotic factors can nevertheless yield a hypothesis to explain the contrasting results between the two regions. Indeed, two transmission routes, not competitively exclusive, may coexist for *MU* colonization of aquatic organisms, through a trophic transmission (**Roche et al., 2013a**) and/or a pathogen transmission through infection with free-living stages present in favourable aquatic environments (**Merritt et al., 2010**). In our study, community abundance has opposite effects in Akonolinga and Bankim, while water flow and *pH* suggest contrasted influence of stagnant waters in these regions. These results could suggest that the prevailing transmission modes could be different within these two environmentally distinct regions. Transmission could be mainly environmentally mediated in Bankim, since stagnant waters, through weak water flows and optimal physico-chemical conditions, are strongly associated with *MU* presence. Furthermore, a lack of association of *MU* abundance with specific taxa in addition to strong positive associations with host diversity and abundance under these favourable conditions, suggests that infection probability in these environments is density dependent, a characteristic feature of this type of transmission (**Codeço, 2001**). Conversely, in Akonolinga, trophic transmission may be expected since optimal abiotic conditions are not met in stagnant ecosystems, and host abundance has a negative impact on *MU* presence, suggesting that presence of some taxa, at least Gastropoda and Hemiptera, can limit transmission in aquatic communities. These alternative transmission routes proposed for *MU* to persist and thrive in aquatic ecosystems could partly explain why BU distribution in humans is greatly associated with stagnant ecosystems but expands over larger geographical regions (**Brou et al., 2008**; **Wagner et al., 2008**; **Jacobsen and Padgett, 2010**; **Marion et al., 2011**).

Our results demonstrate the complex interplay between abiotic and biotic factors driving the dynamics of multi-host/multi-environment diseases. By studying and comparing savannah- and rainforest-like regions, we provide a comprehensive ecological picture of *MU*, that is, a unified framework that reconciles the many contrasting findings observed during the last decade that could apply to a broader geographical area in the tropics and could help us understand the risk of BU for human populations. This study provides a new illustration of emerging infectious diseases for which further investigations looking for a 'bigger picture' are clearly needed in order to cope with the complexity of local and regional environmental situations, and different-scale processes. Judging by the number and importance of multi-host and environmentally persistent pathogens in the total number of emerging infectious diseases appeared in the last four decades such hypotheses deserve to be rigorously tested across multiple epidemiological systems and diverse local conditions. More comprehensive environmental studies in other contexts are needed to assess the generalizability of our findings.

Materials and methods

Environmental data collection

Data were collected as described in ***Garchitorena et al. (2014)***. Briefly, between June 2012 and May 2013, periodic sampling in aquatic ecosystems was performed monthly in Akonolinga and every 3 months in Bankim, two regions in Cameroon where BU is endemic. Akonolinga health district is located in the Centre Province, where rainforest is predominant all across the region. Bankim, on the other hand, is a health district located in the Adamaoua Province, near the border with Nigeria, in a transition zone between forest and savannah. In all, 32 water sites were selected (16 in each region), including a large variety of streams, rivers, swamps, and flooded areas.

Aquatic macro-invertebrates and vertebrates

In each water body, four locations were chosen in areas of slow water flow and among the dominant aquatic vegetation. At each location, five sweeps were done with a metallic dip net (32 × 32 cm, 1 mm mesh size) within a surface of 1 m^2 and at different depth levels. All aquatic organisms collected were identified, classified with the use of taxonomic keys and a binocular microscope, and put separately into tubes with 70% ethanol.

Physico-chemical characteristics of water bodies

Quantitative measures of the water included turbidity (Secchi disc), *pH*, dissolved oxygen, conductivity, and temperature (Multi 3430 with SenTix 940, TetraCon 925, and FDO 925 probes, WTW, Germany). Measures with the probes were taken at 0.5 m depth and only stable values were reported. Test strips for phosphates, iron, and sulfates (Merckoquant, Germany) were used to measure specific ion concentrations near the sediment–water interface. Water flow was assessed visually by measuring the speed of a floating object over the water surface.

M. ulcerans DNA extraction, purification, and detection

Aquatic organisms from the same site and month were pooled for qPCR analysis by groups belonging to the same taxonomic group. At least six sample pools containing the most abundant taxonomic orders were analysed per site and month. Pooled individuals were all ground together and homogenized. DNA from homogenized insect tissues was purified using QIAquick 96 PCR Purification Kit (Qiagen, France). Amplification and detection were performed by quantitative PCR of the gene sequence encoding the ketoreductase B domain (KR) of the mycolactone polyketide synthase (***Rondini et al., 2003***; ***Fyfe et al., 2007***) and the GenBank IS*2404* sequence (***Rondini et al., 2003***). At least 10% negative controls were included during the purification and amplification steps for each assay. Samples were considered positive only when both sequences were detected, with threshold cycle values strictly <35 cycles (see ***Garchitorena et al., 2014*** for details on pooling strategies and PCR analysis).

Data analysis

Statistical model

The proportion of *M. ulcerans* positive sample pools at each sample collection (one site and month) was modelled using binomial regressions in GLMMs (***Zuur et al., 2009***). Since repeated samples were taken from the same sites at regular intervals during one year, we introduced the collection site as a random intercept to control for within-site correlations. In this model, we studied the effect of seasonality, physico-chemical characteristics of the water, and community composition (***Table 4***), all of which were introduced as fixed effects without interactions.

Multi-model selection and inference

Multi-model inference is increasingly recognised as an alternative approach to the use of null hypothesis testing (***Burnham and Anderson, 2002***; ***Grueber et al., 2011***). This approach allows exploring a comprehensive set of potential models obtained as a result of multiple combinations of the explanatory variables. Instead of considering a unique final model, as is the case in classical forward, backward, or stepwise model selection procedures, with multi-model selection, it is possible to identify a set of 'top models' that can be ranked and weighted according to information criteria such as AIC. Model averaging within this set of top models provides quantitative measures of each variable's relative importance (Akaike Weights, w_i) and allows obtaining robust parameter estimates

Table 4. Description of explanatory variables from our environmental data set and their usage in the statistical model

Variable	Min	Max	Median	Prop. zeros	Prop. NAs		Usage
Physico-chemical parameters							
Temperature	20.9	30.2	23	0	0	–	Raw
pH	4.5	7.1	5.5	0	0	–	Log
Dissolved oxygen	0.01	7.6	2	0	0	–	Log
Conductivity	10.2	110.6	22.7	0	0	–	Log
Water flow	0	0.5	0.03	0.34	0.01	–	Categorical
Turbidity	2	250	50	0.19	0.19	–	Removed
Iron	0	10	–	0	0	–	Categorical
Phosphates	0	250	–	0.07	0.07	–	Removed
Sulphates	0	600	–	0.22	0.22	–	Removed
Aquatic community							
Abondance	46	10,591	686.5	0	0	–	Log
Shannon	0.35	2.34	1.7	0	0	–	Raw
Aquatic taxa (%)							
Fish	0	0.32	0	0.32	0	Aquatic	Log
Anura	0	0.54	0	0.33	0	Aquatic	Log
Gastropoda	0	0.8	0	0.37	0	Aquatic	Log
Bivalvia	0	0.13	0	0.91	0	Aquatic	Removed
Araneae	0	0.3	0.01	0.01	0	Terrestrial	Removed
Decapoda	0	0.59	0	0.68	0	Aquatic	Dichotomous
Odonata	0	0.54	0.11	0.02	0	Aquatic	Log
Ephemeroptera	0	0.78	0.16	0.03	0	Aquatic	Log
Hemiptera	0	0.41	0.08	0	0	Aquatic	Log
Trichoptera	0	0.19	0	0.35	0	Aquatic	Log
Lepidoptera	0	0.12	0	0.44	0	Terrestrial	Removed
Plecoptera	0	0.01	0	0.92	0	Aquatic	Removed
Oligochaeta	0	0.18	0	0.69	0	Aquatic	Dichotomous
Hirudinea	0	0.45	0	0.58	0	Aquatic	Dichotomous
Coleoptera	0.01	0.94	0.1	0	0	Aquatic	Log
Diptera	0	0.79	0.15	0	0	Aquatic	Log
Hydracarina	0	0.11	0	0.31	0	Aquatic	Log
Collembola	0	0.06	0	0.4	0	Terrestrial	Removed
Cladocera	0	0.24	0	0.47	0.63	Aquatic	Removed

DOI: 10.7554/eLife.07616.010

and addressing the uncertainty associated with them (***Burnham and Anderson, 2002***). This methodology can be particularly appropriate in the study of complex ecological systems, where multiple interactions take place, and the interest is in finding strong and consistent predictors of a particular outcome. In our study, variables with a relative importance (w_i) larger than 0.8 in these sets of best models and with consistent sign (positive or negative) within the CI were considered to have strong support as predictors of *MU* positivity (***Calcagno, 2013***).

Multi-model selection of GLMMs generated with the package 'lme4' (***Bates et al., 2013***) was performed using the package 'GLMulti' (***Calcagno, 2013***) in R statistical software (***R Development Core Team, 2011***), which uses a genetic algorithm to improve the efficiency of model selection. Within the set of the 100 best models found, only those with an AIC within 2 units difference from the

best model were considered (**Bolker, 2008**). The package 'AICcmodavg' (**Mazerolle, 2013**) was used to estimate model-averaged fixed effects, unconditional standard errors, and 95% CIs. In addition to the set of models obtained using multi-model selection procedures as described above, we used classical forward–backwards selection procedures to provide complementary information and to strengthen the results obtained in this section (Appendix 1, section 1).

Hypotheses and use of variables

Effect of seasonality on MU

Several studies have reported seasonal variations in *MU* positivity, which could reflect an indirect influence of climate mediated through temporal changes in abiotic conditions and abundance of aquatic organisms, or a direct influence, mediated through wash-off of *MU* to the aquatic environment or increased water availability. By including a seasonal effect in a model where temporal changes in abiotic and biotic factors are taken into account, a significant independent effect of seasonality would suggest a direct impact of climate on *MU*. Seasonality was included in the model by transforming the month of collection with *sine* and *cosine* functions with different frequencies (seasonality of 4 or 12 months), as previously described (**Stolwijk et al., 1999**; **Christiansen et al., 2012**). Furthermore, the association of these seasonal functions with observed patterns of monthly and cumulative rainfall in the region was investigated to provide a biological explanation to this potential seasonal effect.

Effect of abiotic conditions on MU

Abiotic water conditions could have a direct effect on *MU*, allowing it to grow or persist as free-living stages, or an indirect effect, through their influence on community composition. By including them in a model that takes into account the impact of aquatic taxa on *MU*, a significant independent effect of abiotic factors would suggest that these conditions are favourable to *MU* growth or persistence. Physico-chemical characteristics of water bodies were log transformed when necessary to approximate a Gaussian distribution (*pH*, dissolved oxygen, conductivity). We also transformed water flow into a categorical variable with three levels, stagnant (0 m/s), lentic (0–0.1 m/s), and lotic (>0.1 m/s). In addition to their individual effect, since several water characteristics correlate and define specific environments, we performed a PCA (using the correlation matrix) on the most relevant physico-chemical parameters (water flow, temperature, dissolved oxygen, and *pH*), and the loadings of the three PCs were included in the analysis as explanatory variables in order to remove the co-linearity between them. Finally, variables with more than 5% missing values (turbidity, phosphates, and sulphates) were discarded in the multivariate analysis to allow for comparable AICs during model selection.

Effect of biotic interactions on MU

The multi-host nature of *MU* implies that, through biotic interactions, individual taxa as well as community-level factors could influence *MU* prevalence. By studying these factors in combination with abiotic conditions, we can not only identify the most relevant ones but also gain insight into the contribution of the two *MU* transmission routes previously described. For instance, a positive *MU* association with community abundance or diversity in environments with favourable conditions would be suggestive of density dependent or direct transmission. On the contrary, if trophic transmission was the main transmission route, likely in environments with unfavourable conditions, *MU* could be positively or negatively associated with host taxa depending on their competency. To study community composition, we calculated total abundance and Shannon index (at the taxonomic order level) for each aquatic community. Relative abundance of each aquatic taxon (taxon abundance/total abundance) was also included. Since total and relative abundance of aquatic taxa were Poisson distributed, these were log transformed to avoid problems related to the skewness of variable distributions. Furthermore, the less abundant aquatic taxa (with more than 40% zero values) were introduced as dichotomous variables, and we removed the very rare taxa (with more than 90% zero values; essentially Plecoptera and Bivalvia). Semi-aquatic or terrestrial taxa collected during the aquatic sampling (Lepidoptera, Araneae, Collembola) were not included either, since they are not likely to play an important role in the aquatic community. Finally, the taxon Cladocera, with more than 5% missing values, was also discarded.

Acknowledgements

We are grateful to Roger Kamgang and Joachim Ossomba at Centre Pasteur du Cameroun for their contribution to the data collection and Jérémie Babonneau and Myriam Benhalima at INSERM for their contribution to the molecular analysis of samples. Thanks to all the members of the consortium ANR-EXTRA MU (Arnaud Fontanet, Jordi Landier, Gaëtan Texier, Philippe Le Gall, Estelle Marion, Danny Lo Seen) for their support and insightful discussions. We are thankful to Gabriel Garcia Peña and Kevin Carolan for advice during data analysis and comments on the first version of the manuscript.

Additional information

Funding

Funder	Grant reference	Author
Agence Nationale de la Recherche	ANR 11 CEPL 007 04 EXTRA-MU	Andrés Garchitorena, Jean-François Guégan, Lucas Léger, Sara Eyangoh, Laurent Marsollier, Benjamin Roche
École des hautes études en santé publique		Andrés Garchitorena, Jean-François Guégan
Institut de recherche pour le développement	JEAI AtoMyc	Andrés Garchitorena, Jean-François Guégan, Sara Eyangoh
Fondation Raoul Follereau		Laurent Marsollier
Institut national de la santé et de la recherche médicale	Programme Inserm Avenir, AtOMycA	Laurent Marsollier
Region Pays de la Loire	ARMINA project	Laurent Marsollier
Fondation pour la Recherche Médicale	FDT20130928241	Laurent Marsollier

The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

Author contributions

AG, Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting or revising the article; J-FG, SE, Conception and design, Drafting or revising the article; LL, Analysis and interpretation of data, Drafting or revising the article; LM, Drafting or revising the article, Contributed unpublished essential data or reagents; BR, Conception and design, Analysis and interpretation of data, Drafting or revising the article

References

Bates D, Maechler M, Bolker B, Walker S. 2013. *lme4: Linear mixed-effects models using Eigen and S4.* R package version 1.0-5, http://CRAN.R-project.org/package=lme4.

Benbow ME, Williamson H, Kimbirauskas R, Mcintosh MD, Kolar R, Quaye C, Akpabey F, Boakye D, Small P, Merritt RW. 2008. Aquatic invertebrates as unlikely vectors of Buruli ulcer disease. *Emerging Infectious Diseases* **14**:1247–1254. doi: 10.3201/eid1408.071503.

Bolker BM. 2008. *Ecological models and data in R.* Princeton: Princeton University Press.

Brou T, Broutin H, Elguero E, Asse H, Guegan JF. 2008. Landscape diversity related to Buruli ulcer disease in Côte d'Ivoire. *PLOS Neglected Tropical Diseases* **2**:e271. doi: 10.1371/journal.pntd.0000271.

Burnham KP, Anderson DR. 2002. *Model selection and multi-model inference: a practical information-theoretic approach.* 2nd edition, New York: Springer.

Calcagno V. 2013. *Glmulti: Model Selection and Multimodel Inference Made Easy. R Package.* R package version 1.0.7, http://cran.r-project.org/web/packages/glmulti/glmulti.pdf.

Christiansen CF, Pedersen L, Sørensen HT, Rothman KJ. 2012. Methods to assess seasonal effects in epidemiological studies of infectious diseases—exemplified by application to the occurrence of meningococcal disease. *Clinical Microbiology and Infection* **18**:963–969. doi: 10.1111/j.1469-0691.2012.03966.x.

Codeço CT. 2001. Endemic and epidemic dynamics of cholera: the role of the aquatic reservoir. *BMC Infectious Diseases* **1**:1. doi: 10.1186/1471-2334-1-1.

Dega H, Robert J, Bonnafous P, Jarlier V, Grosset J. 2000. Activities of several antimicrobials against *Mycobacterium ulcerans* infection in mice. *Antimicrobial Agents and Chemotherapy* **44**:2367–2372. doi: 10.1128/AAC.44.9.2367-2372.2000.

Dickens CWS, Graham PM. 2002. The South African scoring system (SASS) version 5 rapid bioassessment method for rivers. *African Journal of Aquatic Science* **27**:1–10. doi: 10.2989/16085914.2002.9626569.

Doig KD, Holt KE, Fyfe JA, Lavender CJ, Eddyani M, Portaels F, Yeboah-Manu D, Pluschke G, Seemann T, Stinear TP. 2012. On the origin of *Mycobacterium ulcerans*, the causative agent of Buruli ulcer. *BMC Genomics* **13**:258. doi: 10.1186/1471-2164-13-258.

Eric Benbow M, Kimbirauskas R, McIntosh MD, Williamson H, Quaye C, Boakye D, Small PL, Merritt RW. 2013. Aquatic macroinvertebrate assemblages of Ghana, West Africa: understanding the ecology of a neglected tropical disease. *EcoHealth* **11**:168–183. doi: 10.1007/s10393-013-0886-7.

Ezenwa VO, Godsey MS, King RJ, Guptill SC. 2006. Avian diversity and West Nile virus: testing associations between biodiversity and infectious disease risk. *Proceedings. Biological Sciences/The Royal Society* **273**:109–117. doi: 10.1098/rspb.2005.3284.

Fyfe JA, Lavender CJ, Johnson PD, Globan M, Sievers A, Azuolas J, Stinear TP. 2007. Development and application of two multiplex real-time PCR assays for the detection of *Mycobacterium ulcerans* in clinical and environmental samples. *Applied and Environmental Microbiology* **73**:4733–4740. doi: 10.1128/AEM.02971-06.

Garchitorena A, Roche B, Kamgang R, Ossomba J, Babonneau J, Landier J, Fontanet A, Flahault A, Eyangoh S, Guégan JF, Marsollier L. 2014. *Mycobacterium ulcerans* ecological dynamics and its association with freshwater ecosystems and aquatic communities: results from a 12-month environmental survey in Cameroon. *PLOS Neglected Tropical Diseases* **8**:e2879. doi: 10.1371/journal.pntd.0002879.

Grueber CE, Nakagawa S, Laws RJ, Jamieson IG. 2011. Multimodel inference in ecology and evolution: Challenges and solutions. *Journal of Evolutionary Biology* **24**:699–711. doi: 10.1111/j.1420-9101.2010.02210.x.

Hennigan CE, Myers L, Ferris MJ. 2013. Environmental distribution and seasonal prevalence of *Mycobacterium ulcerans* in Southern Louisiana. *Applied and Environmental Microbiology* **79**:2648–2656. doi: 10.1128/AEM.03543-12.

Jacobsen KH, Padgett JJ. 2010. Risk factors for *Mycobacterium ulcerans* infection. *International Journal of Infectious Diseases* **14**:e677–e681. doi: 10.1016/j.ijid.2009.11.013.

Johnson PT, Preston DL, Hoverman JT, Richgels KL. 2013. Biodiversity decreases disease through predictable changes in host community competence. *Nature* **494**:230–233. doi: 10.1038/nature11883.

Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, Daszak P. 2008. Global trends in emerging infectious diseases. *Nature* **451**:990–993. doi: 10.1038/nature06536.

Keesing F, Belden LK, Daszak P, Dobson A, Harvell CD, Holt RD, Hudson P, Jolles A, Jones KE, Mitchell CE, Myers SS, Bogich T, Ostfeld RS. 2010. Impacts of biodiversity on the emergence and transmission of infectious diseases. *Nature* **468**:647–652. doi: 10.1038/nature09575.

LoGiudice K, Ostfeld RS, Schmidt KA, Keesing F. 2003. The ecology of infectious disease: effects of host diversity and community composition on Lyme disease risk. *Proceedings of the National Academy of Sciences of USA* **100**:567–571. doi: 10.1073/pnas.0233733100.

Marion E, Eyangoh S, Yeramian E, Doannio J, Landier J, Aubry J, Fontanet A, Rogier C, Cassisa V, Cottin J, Marot A, Eveillard M, Kamdem Y, Legras P, Deshayes C, Saint-André JP, Marsollier L. 2010. Seasonal and regional dynamics of *M. ulcerans* transmission in environmental context: deciphering the role of water bugs as hosts and vectors. *PLOS Neglected Tropical Diseases* **4**:e731. doi: 10.1371/journal.pntd.0000731.

Marion E, Landier J, Boisier P, Marsollier L, Fontanet A, Le Gall P, Aubry J, Djeunga N, Umboock A, Eyangoh S. 2011. Geographic expansion of Buruli ulcer disease, Cameroon. *Emerging Infectious Diseases* **17**:551–553. doi: 10.3201/eid1703.091859.

Marsollier L, André JP, Frigui W, Reysset G, Milon G, Carbonnelle B, Aubry J, Cole ST. 2007a. Early trafficking events of *Mycobacterium ulcerans* within *Naucoris Cimicoides*. *Cellular Microbiology* **9**:347–355. doi: 10.1111/j.1462-5822.2006.00790.x.

Marsollier L, Aubry J, Coutanceau E, André JP, Small PL, Milon G, Legras P, Guadagnini S, Carbonnelle B, Cole ST. 2005. Colonization of the salivary glands of *Naucoris cimicoides* by *Mycobacterium ulcerans* requires host plasmatocytes and a macrolide toxin, mycolactone. *Cellular Microbiology* **7**:935–943. doi: 10.1111/j.1462-5822.2005.00521.x.

Marsollier L, Brodin P, Jackson M, Korduláková J, Tafelmeyer P, Carbonnelle E, Aubry J, Milon G, Legras P, André JP, Leroy C, Cottin J, Guillou ML, Reysset G, Cole ST. 2007b. Impact of *Mycobacterium ulcerans* biofilm on transmissibility to ecological niches and Buruli ulcer pathogenesis. *PLOS Pathogens* **3**:e62. doi: 10.1371/journal.ppat.0030062.

Marsollier L, Robert R, Aubry J, Saint Andre JP, Kouakou H, Legras P, Manceau AL, Mahaza C, Carbonnelle B. 2002. Aquatic insects as a vector for *Mycobacterium ulcerans*. *Applied and Environmental Microbiology* **68**:4623–4628. doi: 10.1128/AEM.68.9.4623.

Marsollier L, Sévérin T. 2004. Aquatic snails, passive hosts of *Mycobacterium ulcerans*. *Applied and Environmental Microbiology* **70**:6296–6298. doi: 10.1128/AEM.70.10.6296-6298.2004.

Marsollier L, Stinear T, Aubry J, Saint Andre JP, Robert R, Legras P, Manceau AL, Audrain C, Bourdon S, Kouakou H, Carbonnelle B. 2004. Aquatic plants stimulate the growth of and biofilm formation by *Mycobacterium ulcerans* in axenic culture and harbor these bacteria in the environment. *Applied and Environmental Microbiology* **70**:1097–1103. doi: 10.1128/AEM.70.2.1097.

Mazerolle MJ. 2013. *AICcmodavg: Model Selection and Multimodel Inference Based on (Q)AIC(c). R Package.* R package version 1.35, http://cran.r-project.org/web/packages/AICcmodavg/AICcmodavg.pdf.
Merritt RW, Walker ED, Small PL, Wallace JR, Johnson PD, Benbow ME, Boakye DA. 2010. Ecology and transmission of Buruli ulcer disease: a systematic review. *PLOS Neglected Tropical Diseases* **4**:e911. doi: 10.1371/journal.pntd.0000911.
Morris A, Gozlan RE, Hassani H, Andreou D, Couppié P, Guégan JF. 2014. Complex temporal climate signals drive the emergence of human water-borne disease. *Emerging Microbes & Infections* **3**:e56. doi: 10.1038/emi.2014.56.
Mosi L, Williamson H, Wallace JR, Merritt RW, Small PL. 2008. Persistent association of *Mycobacterium ulcerans* with West African predaceous insects of the family belostomatidae. *Applied and Environmental Microbiology* **74**: 7036–7042. doi: 10.1128/AEM.01234-08.
Ostfeld RS, Keesing F, Eviner VT. 2008. *Infectious disease ecology: effects of ecosystems on disease and of disease on ecosystems.* Princeton: Princeton University Press.
Palomino JC, Obiang AM, Realini L, Meyers WM, Portaels F. 1998. Effect of oxygen on growth of *Mycobacterium ulcerans* in the BACTEC system. *Journal of Clinical Microbiology* **36**:3420–3422.
Palomino JC, Portaels F. 1998. Effects of decontamination methods and culture conditions on viability of *Mycobacterium ulcerans* in the BACTEC system. *Journal of Clinical Microbiology* **36**:402–408.
Plowright RK, Sokolow SH, Gorman ME, Daszak P, Foley JE. 2008. Causal inference in disease ecology: investigating ecological drivers of disease emergence. *Frontiers in Ecology and the Environment* **6**:420–429. doi: 10.1890/070086.
Portaels F, Pattyn SR. 1982. Growth of mycobacteria in relation to the pH of the medium. *Annales de Microbiologie* **133**:213–221.
R Development Core Team. 2011. *R: A language and environment for statistical computing.* Vienna, Austria: R Foundation for Statistical Computing.
Roche B, Benbow ME, Merritt R, Kimbirauskas R, McIntosh M, Small PL, Williamson H, Guégan JF. 2013a. Identifying the Achilles' heel of multi-host pathogens: the concept of keystone 'host' species illustrated by *Mycobacterium ulcerans* transmission. *Environmental Research Letters* **8**:045009. doi: 10.1088/1748-9326/8/4/045009.
Roche B, Rohani P, Dobson AP, Guégan JF. 2013b. The impact of community organization on vector-borne pathogens. *The American Naturalist* **181**:1–11. doi: 10.1086/668591.
Roche B, Guégan JF. 2011. Ecosystem dynamics, biological diversity and emerging infectious diseases. *Comptes Rendus Biologies* **334**:(5-6):385–392. doi: 10.1016/j.crvi.2011.02.008.
Rondini S, Mensah-Quainoo E, Troll H, Bodmer T, Pluschke G. 2003. Development and application of real-time PCR assay for quantification of *Mycobacterium ulcerans* DNA. *Journal of Clinical Microbiology* **41**:4231–4237. doi: 10.1128/JCM.41.9.4231.
Stinear TP, Seemann T, Pidot S, Frigui W, Reysset G, Garnier T, Meurice G, Simon D, Bouchier C, Ma L, Tichit M, Porter JL, Ryan J, Johnson PD, Davies JK, Jenkin GA, Small PL, Jones LM, Tekaia F, Laval F, Daffé M, Parkhill J, Cole ST. 2007. Reductive evolution and niche adaptation inferred from the genome of *Mycobacterium ulcerans*, the causative agent of Buruli ulcer. *Genome Research* **17**:192–200. doi: 10.1101/gr.5942807.
Stolwijk AM, Straatman H, Zielhuis GA. 1999. Studying seasonality by using sine and cosine functions in regression analysis. *Journal of Epidemiology and Community Health* **53**:235–238. doi: 10.1136/jech.53.4.235.
Suzán G, Marcé E, Giermakowski JT, Mills JN, Ceballos G, Ostfeld RS, Armién B, Pascale JM, Yates TL. 2009. Experimental evidence for reduced rodent diversity causing increased hantavirus prevalence. *PLOS ONE* **4**: e5461. doi: 10.1371/journal.pone.0005461.
Wagner T, Benbow ME, Brenden TO, Qi J, Johnson RC. 2008. Buruli ulcer disease prevalence in Benin, West Africa: associations with land use/cover and the identification of disease clusters. *International Journal of Health Geographics* **7**:25. doi: 10.1186/1476-072X-7-25.
WHO. 2008. *Buruli ulcer: progress report, 2004–2008. Weekly epidemiological record,* **Volume 336**. Geneva, Switzerland.
Woolhouse ME, Gowtage-Sequeria S. 2005. Host range and emerging and reemerging pathogens. *Emerging Infectious Diseases* **11**:1842–1847. doi: 10.3201/eid1112.050997.
Woolhouse ME, Taylor LH, Haydon DT. 2001. Population biology of multihost pathogens. *Science* **292**:1109–1112. doi: 10.1126/science.1059026.
Zuur AF, Ieno EN, Walker NJ, Saveliev AA, Smith GM. 2009. *Mixed effects models and extensions in ecology with R.* New York: Springer Science.

Appendix 1

Section 1: backwards–forward model selection

The multi-model selection approach was chosen for its improved capabilities when compared to standard selection approaches, since it allows accounting for and describing the uncertainty in the parameters due to model selection. As a result, this approach and its results for each region are described in the main text. In this section, we describe the methodology and results of additional analyses using a classical forward–backward selection approach. We demonstrate that this selection procedure gives comparable results to those from the multi-model selection described in the main text.

Methodology

A combination of backward and forward procedures based on Akaike's Information Criteria (AIC) and likelihood ratio tests was used to select the final multivariate model. Firstly, all variables were tested individually as fixed effects in univariate binomial regressions with the site of collection as random effect. Those variables showing a significant effect were retained for an initial multivariate model. A backward procedure was then applied on this initial model in order to select, one by one, the variables that did not significantly improve the model (based on likelihood ratio tests) and, among these, we dropped those variables that resulted in the model with the lowest AIC. Secondly, a forward procedure was carried out by adding to this reduced model, one by one, all variables that significantly improved the model (likelihood ratio test) and, among those, those that resulted in the model with the lowest AIC. At each step, we checked whether the addition of the new variable made others insignificant, in which case, we dropped those variables from the model. The final model was obtained when no significant improvement could be achieved with the addition of new variables. Violation of model assumptions was checked in the final models. Colinearity was assessed through graphical exploration of explanatory variables, correlation tests, and variance inflation factors (VIF) in the final model. Independence was assessed by studying the spatial (correlograms) and temporal correlation (cross-correlations) of the model residuals.

Multivariate results

Similarly to the results obtained with multi-model selection, a combination of seasonal factors, water conditions, and community composition remained in the final models for Akonolinga and Bankim (***Appendix table 1***). Firstly, the effect of seasonality remained for Akonolinga after accounting for water parameters and biological factors. Secondly, regarding water conditions, *pH* had a significant positive effect on *MU* presence in Akonolinga, whereas in Bankim the negative effect of water flow was evident, with lotic ecosystems being the least positive, followed by lentic ones, which had significantly lower positivity than stagnant ecosystems. Finally, the effect of aquatic communities through total abundance was significant and inversely correlated with *MU* in Akonolinga, while in Bankim Shannon's diversity showed a positive correlation with *MU* presence. Individual taxa that remained significant and inversely correlated with *MU* were Gastropoda, Decapoda, Hemiptera and Anura for Akonolinga; and Ephemeroptera, fish, Diptera and Anura for Bankim. The only taxon positively correlated with *MU* in the final model was Hirudinea in Akonolinga and Coleoptera for Bankim. In summary, the results obtained from multi-model selection and classical model selection procedures were qualitatively and quantitatively similar.

Appendix table 1. Results of multivariate analyses for Akonolinga (12 months of sampling) and Bankim (4 months of sampling)

	Akonolinga (n = 183)			Bankim (n = 61)		
Variable	**Effect**	**Std. error**	**p-value**	**Effect**	**Std. error**	**p-value**
Model AIC	400.7	–	–	182.7	–	–
Variance of random effect	0.20	–	–	1.77	–	–
(Intercept)	−12.56	4.40	<0.001	−7.40	1.97	<0.001
Seasonality						
Sine(2pi*Month/12)	0.34	0.14	0.02	–	–	–
Sine(2pi*Month/4)	–	–	–	–	–	–
Cos(2pi*Month/12)	–	–	–	–	–	–
Cos(2pi*Month/4)	–	–	–	–	–	–
Physico-chemical parameters						
Temperature	–	–	–	–	–	–
pH	8.63	2.44	<0.001	–	–	–
Dissolved oxygen	–	–	–	–	–	–
Conductivity	–	–	–	–	–	–
Iron	–	–	–	–	–	–
Water flow (Lentic)	–	–	–	−2.10	0.47	<0.001
Water flow (Lotic)	–	–	–	−3.18	0.69	<0.001
Physico-chemical parameters (PCA)						
PC1	–	–	–	–	–	–
PC2	–	–	–	–	–	–
PC3	–	–	–	–	–	–
Community						
Abundance	−0.64	0.17	<0.001	–	–	–
Shannon	–	–	–	4.16	0.97	<0.001
Orders (%)						
Fish	–	–	–	−1.62	0.35	<0.001
Anura	−0.34	0.14	0.02	−0.84	0.32	0.01
Gastropoda	−0.64	0.16	<0.001	–	–	–
Decapoda (presence)	−1.37	0.37	<0.001	–	–	–
Odonata	–	–	–	–	–	–
Ephemeroptera	–	–	–	−0.94	0.21	<0.001
Hemiptera	−0.47	0.20	0.02	–	–	–
Tricoptera	–	–	–	–	–	–
Oligochaeta (presence)	–	–	–	–	–	–
Hirudinea (presence)	0.59	0.23	0.01	–	–	–
Coleoptera	–	–	–	–	–	–
Diptera	–	–	–	1.08	0.36	<0.001
Hydracarine	–	–	–	−1.58	0.49	<0.001

The models used are Binomial regressions with random effect site, selected with forward–backwards procedure (see section 1 for details).

DOI: 10.7554/eLife.07616.011

Section 2: differences in communities in Akonolinga and Bankim

In the main text, we justify the different results obtained for Akonolinga and Bankim partly based on differences between the two regions, both in terms of physico-chemical parameters and community composition (***Figure 3***). In ***Appendix table 2***, we show the relative abundance for each taxonomic group in each region and test for differences on the mean relative abundance between the regions by using Mann–Whitney tests (also known as Wilcoxon rank-sum tests).

Appendix table 2. Differences in community composition between Akonolinga and Bankim

Taxonomic group	Relative abundance (%)				Mann–Whitney test
	Akonolinga		Bankim		
	Mean	SD	Mean	SD	p-value
Fish	1.04	2.20	2.39	4.93	<0.001
Anura	2.56	6.62	2.08	6.73	0.009
Gastropoda	2.70	7.76	3.41	9.33	0.449
Bivalvia	0.19	1.08	0.00	0.03	0.016
Decapoda	5.36	12.37	0.90	2.78	0.010
Odonata	12.72	9.96	15.79	15.03	0.616
Ephemeroptera	21.77	17.22	15.56	14.74	0.010
Hemiptera	8.15	5.85	11.84	8.55	<0.001
Tricoptera	2.62	4.20	1.23	2.23	0.011
Hirudinea	1.29	4.76	2.63	7.31	0.005
Oligochaeta	0.64	1.94	0.67	2.11	0.291
Coleoptera	18.98	20.54	11.99	11.37	0.023
Diptera	17.58	14.23	23.69	16.25	0.004
Hydracarine	0.83	1.38	0.90	1.77	0.171

For each taxon included in the statistical model, the mean and standard deviation (SD) of the relative abundance (%) for each region are given, along with the p-value of a Mann–Whitney test comparing the mean relative abundance in the two regions.

DOI: 10.7554/eLife.07616.012

PHILOSOPHICAL TRANSACTIONS B

rstb.royalsocietypublishing.org

Research

Cite this article: Garchitorena A *et al*. 2017 Disease ecology, health and the environment: a framework to account for ecological and socio-economic drivers in the control of neglected tropical diseases. *Phil. Trans. R. Soc. B* **372**: 20160128.
http://dx.doi.org/10.1098/rstb.2016.0128

Accepted: 3 January 2017

One contribution of 13 to a theme issue 'Conservation, biodiversity and infectious disease: scientific evidence and policy implications'.

Subject Areas:
ecology, environmental science, health and disease and epidemiology

Keywords:
planetary health, environmentally transmitted diseases, coupled ecological–economic systems, sustainable disease control

Author for correspondence:
M. H. Bonds
e-mail: mhb9@hms.harvard.edu

Electronic supplementary material is available online at https://dx.doi.org/10.6084/m9.figshare.c.3716626.

THE ROYAL SOCIETY PUBLISHING

Disease ecology, health and the environment: a framework to account for ecological and socio-economic drivers in the control of neglected tropical diseases

A. Garchitorena[1,2], S. H. Sokolow[3], B. Roche[4,5], C. N. Ngonghala[6], M. Jocque[3], A. Lund[7], M. Barry[8], E. A. Mordecai[9], G. C. Daily[9], J. H. Jones[10,11], J. R. Andrews[12], E. Bendavid[12], S. P. Luby[8], A. D. LaBeaud[13], K. Seetah[14], J. F. Guégan[5,15], M. H. Bonds[1,2,12] and G. A. De Leo[3]

[1]Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA 02115, USA
[2]PIVOT, Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA 02115, USA
[3]Department of Biology, Hopkins Marine Station, Stanford University, Pacific Grove, CA 93950, USA
[4]UMI UMMISCO 209 IRD/UPMC – Bondy, France
[5]UMR MIVEGEC 5290 CNRS - IRD - Université de Montpellier, Montpellier, France
[6]Department of Mathematics, University of Florida, Gainesville, FL 32611, USA
[7]Emmett Interdisciplinary Program in Environment and Resources, [8]Center for Innovation in Global Health, [9]Department of Biology, and [10]Department of Earth System Science, Stanford University, Stanford, CA 94305, USA
[11]Department of Life Sciences, Imperial College, London, UK
[12]Department of Medicine, [13]Department of Pediatrics, Division of Infectious Diseases, and [14]Department of Anthropology, Stanford University, Stanford, CA 94305, USA
[15]Future Earth international programme, OneHealth core research programme, Montréal, Canada

AG, 0000-0001-6225-5226; BR, 0000-0001-7975-4232; JHJ, 0000-0003-1680-6757; MHB, 0000-0002-3055-4237

Reducing the burden of neglected tropical diseases (NTDs) is one of the key strategic targets advanced by the Sustainable Development Goals. Despite the unprecedented effort deployed for NTD elimination in the past decade, their control, mainly through drug administration, remains particularly challenging: persistent poverty and repeated exposure to pathogens embedded in the environment limit the efficacy of strategies focused exclusively on human treatment or medical care. Here, we present a simple modelling framework to illustrate the relative role of ecological and socio-economic drivers of environmentally transmitted parasites and pathogens. Through the analysis of system dynamics, we show that periodic drug treatments that lead to the elimination of directly transmitted diseases may fail to do so in the case of human pathogens with an environmental reservoir. Control of environmentally transmitted diseases can be more effective when human treatment is complemented with interventions targeting the environmental reservoir of the pathogen. We present mechanisms through which the environment can influence the dynamics of poverty via disease feedbacks. For illustration, we present the case studies of Buruli ulcer and schistosomiasis, two devastating waterborne NTDs for which control is particularly challenging.

This article is part of the themed issue 'Conservation, biodiversity and infectious disease: scientific evidence and policy implications'.

1. Introduction

More than one billion people, most of them in tropical and subtropical countries, still live in extreme poverty and suffer a disproportionate burden of neglected tropical diseases (NTDs) [1,2]. NTDs consist of parasitic, viral and bacterial infections (table 1) that are responsible for chronic disabling conditions that account for more than 500 000 deaths and nearly 57 million disability-adjusted life-years

Table 1. NTDs, causes, global burden and current priorities for disease control (based on WHO 2015 [3]).

NTD Group	pathogens responsible	transmission route	disease burden	control target and main strategies[a]
Parasitic infections				
soil-transmitted helminthiases	*Ascaris* spp., *Trichuris* spp., *Necator* spp. and *Ancylostoma* spp.	*Environmental*. Ingestion of eggs and larvae or penetration of the skin	875 million children at risk	*Morbidity control*. MDA of PC (albendazole or mebendazole)
schistosomiasis	*Schistosoma* spp. (mostly *S. haematobium* and *S. japonicum*)	*Waterborne*. Direct entry into skin after asexual multiplication in snail hosts	240 million infected	*Elimination* (some regions). MDA of PC (praziquantel)
lymphatic filariasis	*Wuchereria bancrofti, Brugia malayi* and *B. timori*	*Vector-borne*. Mosquito bites (*Anopheles* spp., *Culex* spp. and *Aedes* spp.)	more than 120 million infected	*Elimination*. MDA of PC (albendazole + diethylcarbamazine or ivermectin)
onchocerciasis	*Onchocerca volvulus*	*Vector-borne*. Bites of blackflies (*Simulium* spp.)	37 million infected	*Elimination*. MDA of PC (ivermectin)
dracunculiasis (Guinea worm)	*Dracunculus medinensis*	*Waterborne*. Drinking water with infected copepods	100–200 cases/year	*Eradication*. Active surveillance, water filters, and improved drinking water sources
foodborne trematodiases	*Clonorchis* spp., *Opisthorchis* spp., *Fasciola* spp. and *Paragonimus* spp.	*Foodborne*. Consumption of contaminated fish, seafood or vegetables	unclear; more than 56 million in 2005	*Morbidity control*. MDA of PC (praziquantel or triclabendazole)
taeniasis/cisticercosis	*Taenia solium*	*Foodborne or faecal–oral*. Consumption of pork or ingestion of parasite eggs	unclear; responsible for 1.5 million epilepsy cases	*Reduce transmission*. Veterinary controls of pork meat; treatment of infected pigs and humans
echinococcosis	*Echinococcus granulosus* and *E. multilocularis*	*Foodborne*. Accidental ingestion of items contaminated with eggs	unclear; 30/100 000 person-year, endemic areas	*Reduce transmission*. Veterinary controls of livestock; dog vaccination and regular treatment
Protozoan infections				
human African trypanosomiasis	*Trypanosoma brucei gambiense* and *T. brucei rhodesiense*	*Vector-borne*. Bites of tse-tse flies (*Glossina* spp.)	20 000 cases/year	*Elimination*. Early diagnosis and treatment (pentamidine, suramin, melarsoprol or eflornithine)
Chagas disease	*Trypanosoma cruzi*	*Vector-borne*. Faeces of haematophagous triatomines	seven million infected	*Reduce transmission*. Sustained vector control; early diagnosis and treatment (benznidazole or nifurtimox)
leishmaniasis	*Leishmania* spp.	*Vector-borne*. Bites of sandflies (*Phlebotomus* spp.)	1.3 million cases/year	*Elimination* (some regions). Surveillance, early diagnosis and treatment (liposomal amphotericin B)
Bacterial infections				
Buruli ulcer	*Mycobacterium ulcerans*	*Waterborne*. Vector-borne and/or direct environmental transmission (unclear)	5000 cases/year	*Prevention of disability*. Early diagnosis and treatment (streptomycin + rifampin)
leprosy	*Mycobacterium leprae*	*Person-to-person*. Skin contact or respiratory route (unclear)	200 000 cases/year	*Elimination*. Early diagnosis and treatment (multidrug therapy)

(*Continued*.)

Table 1. (*Continued.*)

NTD Group	pathogens responsible	transmission route	disease burden	control target and main strategies[a]
trachoma	*Chlamydia trachomatis*	*Person-to-person*. Direct personal contact, shared towels and cloths, or flies	more than 21 million with active trachoma	*Elimination*. MDA of PC (azithromycin)
yaws (endemic treponematoses)	*Treponema pallidum*	*Person-to-person*. Skin contact	50 000–80 000 cases/year	*Eradication*. MDA of PC (azithromycin); early diagnosis and treatment
Viral infections				
dengue and chikungunya	Arbovirus (dengue virus and chikungunya virus)	*Vector-borne*. Mosquito bites (*Aedes* spp.)	390 million dengue infections/year	*Reduce mortality, morbidity and transmission*. Integrated surveillance and vector control
rabies	rabies virus	*Zoonosis*. Bite from infected dogs	60 000 deaths/year	*Elimination*. Mass vaccination of domestic dogs

[a]MDA of PC, mass drug administration of preventive chemotherapy.

(DALYs) annually [4,5]. The availability of affordable and safe drug treatments has led to declines in the prevalence of many NTDs, with plans for the elimination of lymphatic filariasis, onchocerciasis and trachoma by 2030 (table 1) [3,6]. Nevertheless, there is growing recognition of the limitations of interventions focused exclusively on treating the human host [3,7]. Most pathogens responsible for NTDs spend part of their life cycle outside the human host and are transmitted through environmental pathways (table 1), such that people may be repeatedly exposed and infected [7]. Moreover, coverage targets for mass drug administration (MDA) are hard to meet in the context of weak healthcare-delivery systems and extreme poverty, and drug resistance can threaten the long-term success of control programmes [8]. Sustainably reducing the burden of many NTDs requires complementary strategies to disrupt disease transmission that are informed by a broader understanding of interactions taking place in coupled natural–human systems [9].

Here, we present a conceptual framework based on a simple model to account for ecological and socio-economic drivers of NTDs for designing context-specific control strategies. As examples, we present the cases of Buruli ulcer and schistosomiasis, two NTDs associated with land-use change in hydrological ecosystems, which represent different ends of the spectrum of diseases for which transmission is highly dependent on the environment (referred to hereafter as 'environmentally transmitted'). Buruli ulcer is caused by *Mycobacterium ulcerans* which, like other 'sapronotic' pathogens [10], can be considered ubiquitous and free-living within the environment (i.e. not dependent on the level of infection within humans or any other known host) in certain regions. It afflicts only a few thousand people per year, but each case of infection can cause permanent disability with catastrophic socio-economic effects on households. Schistosomiasis, which is caused by *Schistosoma* spp., is representative of a larger class of parasitic worms and vector-borne pathogens whose presence in the environment depends upon the local prevalence of infected people. Schistosomiasis infects hundreds of millions of people each year and is responsible for a high burden of chronic morbidity globally. Integration of ecological knowledge and socio-economic feedbacks into a common framework can thus inform the most effective action targets and lead to better interventions for control of NTDs and other infectious diseases of poverty.

2. A framework for coupled ecological and socio-economic determinants of disease

Economic systems of the rural poor are often coupled with natural systems through subsistence-resource exploitation (e.g. agriculture, pastoralism and fishing) and exposure to ambient pathogens (figure 1) [11,12]. This is particularly relevant in the tropics, where climatic conditions are favourable for many pathogens and their vectors (e.g. flies, mosquitoes and ticks), and the diversity of mammal and bird species hosts a greater diversity of pathogens in this region [13–16]. Land-use change for the purpose of economic development (e.g. expansion of road networks, dams and agricultural land conversion) can further affect environmentally transmitted parasites and pathogens through impacts on physicochemical conditions of water and soil [15], ecological community composition (e.g. loss of biodiversity), or inter- and intra-species interactions (e.g. predation and migration) [17,18].

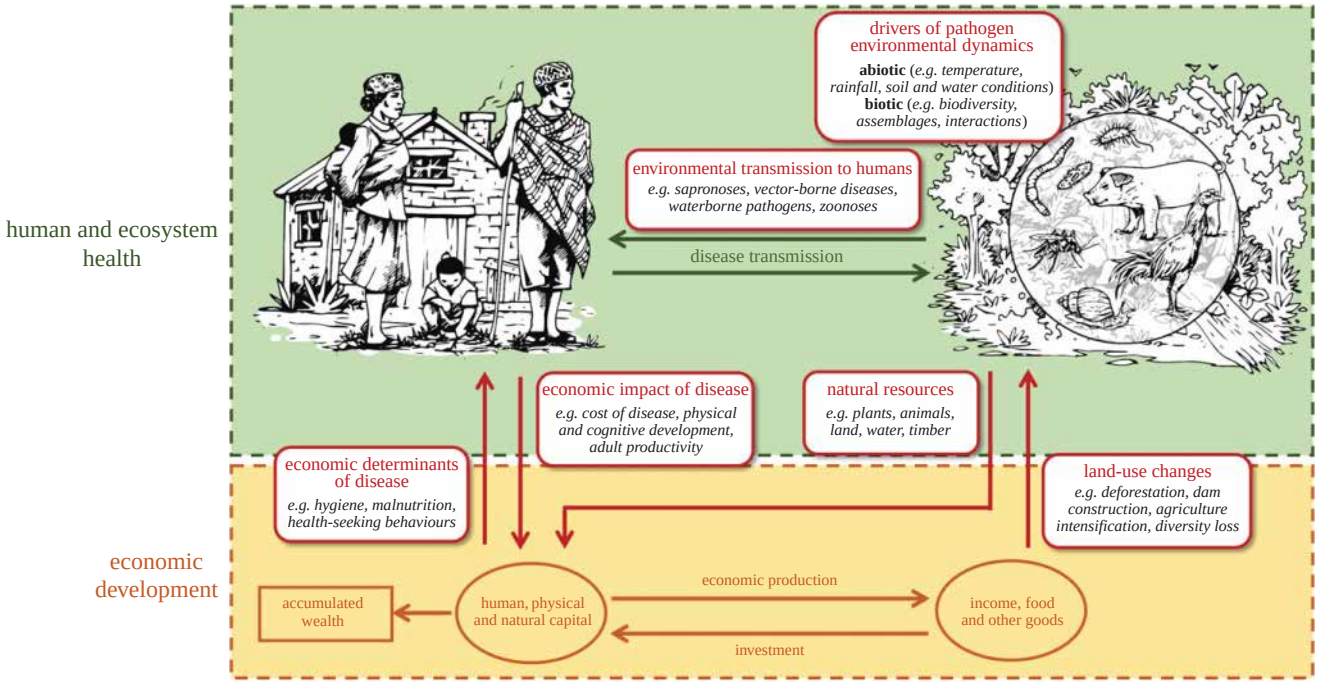

Figure 1. Coupled natural and human systems: feedbacks between ecosystems, infectious diseases and economic development. Many human pathogens in tropical regions, including those that cause NTDs, spend part of their lifecycle outside the human host, where environmental conditions drive their ecology and transmission (upper panel). Ecosystem and disease dynamics influence key forms of capital necessary for economic development of at-risk human communities (lower panel). Simultaneously, economic activities and resources affect those same dynamics by altering vulnerability to disease and introducing land-use change to ecosystems.

(a) Model of environmental transmission of disease

Building on traditional systems in disease ecology and epidemiology [19–21], we first present a general infectious disease model that accounts for direct and environmental pathways of disease transmission. The model is meant to represent the dynamics of NTDs and other tropical diseases of poverty across a wide spectrum of transmission strategies, spanning from human-to-human contagious diseases (e.g. leprosy and trachoma) to parasitic worms (e.g. schistosomiasis), waterborne bacteria (e.g. Buruli ulcer), foodborne pathogens (e.g. echinococcosis), vector-borne diseases (e.g. dengue and malaria), or zoonotic and multi-host pathogens (e.g. rabies and Nipah virus):

$$\frac{dI}{dt} = [\beta_E W + \beta_D I]S - \gamma I \tag{2.1a}$$

and

$$\frac{dW}{dt} = \Omega + V\sigma\lambda I - \delta W. \tag{2.1b}$$

The state variables I and S represent the infected and susceptible proportions of the human population, respectively; W is the environmental reservoir of the pathogen; β_D is the direct (human-to-human) transmission rate; β_E is the transmission rate through the environmental reservoir; γ is the rate of recovery (either into an immune class in an SIR model or back to the susceptible class in an SIS model without immunity); λ is the rate or production of infectious propagules released in the environment (either as free-living stages, such as for soil-transmitted helminths, or pathogen abundance in vectors or intermediate hosts); σ is the fraction of the propagules that reach the environment; V is a parameter proportional to the abundance of vectors (in the case of dengue, chikungunya, etc.), to the abundance of intermediate hosts (in the case of trematode infections, such as schistosomiasis, fascioliasis, etc.), or to habitat suitability for pathogen environmental persistence (in the case of soil-borne or waterborne diseases, such as intestinal nematode infections and cholera, respectively); Ω is the recruitment rate of infective propagules associated with exogenous processes not directly related to disease prevalence in the population; δ is the mortality of infectious stages in the environment. From this general framework, we define two parameters (or 'meta-parameters') that characterize the role of the environment on transmission:

$$\varepsilon = \frac{\beta_E W}{\beta_E W + \beta_D I} \tag{2.2a}$$

and

$$\varphi = \frac{\Omega}{\Omega + V\sigma\lambda I}. \tag{2.2b}$$

Parameter ε is an index of environmental transmission that ranges from zero for direct transmission (i.e. person-to-person) to unity for complete environmental transmission (i.e. pathogens with obligatory non-human hosts, reservoirs or vectors). Parameter φ represents the degree of exogenous versus focal transmission among the environmentally transmitted diseases (ETDs). It ranges from zero when the abundance of infectious propagules in the environmental reservoir is solely a function of the local number/fraction of infected people, with no exogenous recruitment ($\Omega = 0$ and $\lambda > 0$), to unity when the pathogen's environmental load depends exclusively on its own free-living replication in the environment or on other environmental factors ($\Omega > 0$ and $\lambda = 0$). 'Sapronotic' pathogens—those that can replicate within the environment free of any known host (a characteristic of almost all fungal pathogens, about one-third of bacterial pathogens and several parasites that infect man [10])—have

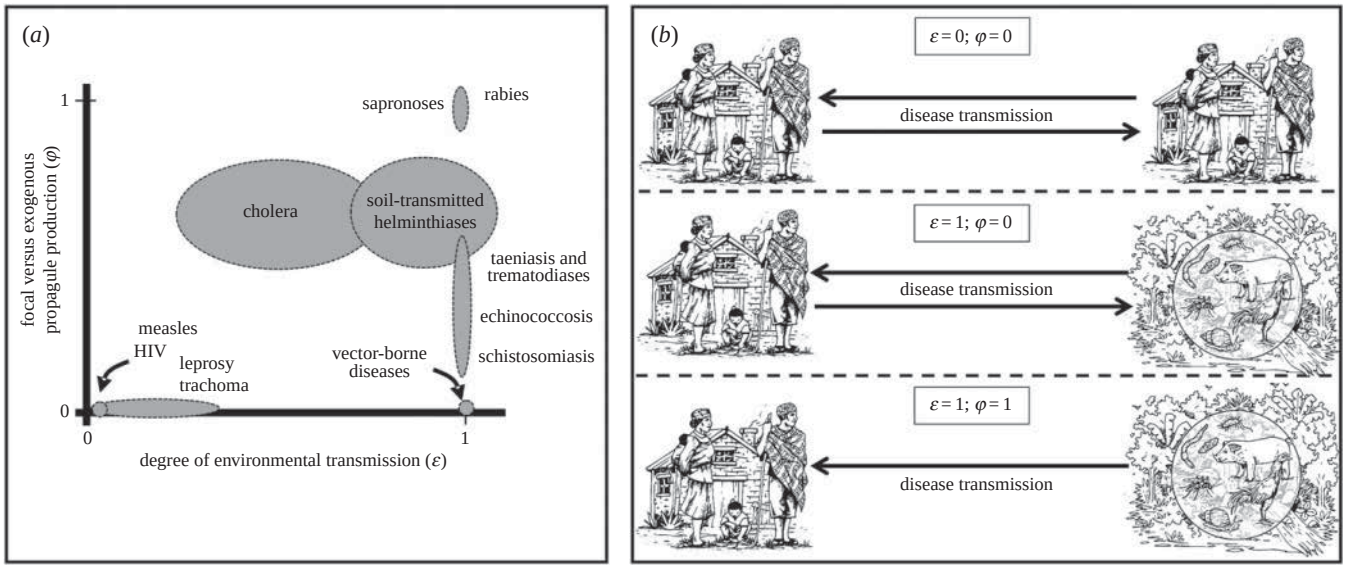

Figure 2. A conceptual framework to account for multiple pathways of disease transmission in coupled economic–epidemiological systems. (*a*) Qualitative classification of relevant infectious and parasitic diseases in developing countries according to two key parameters that regulate environmental transmission in this conceptual framework (ε and φ). Ellipsoids represent educated guesses about the parameter space occupied by each disease, including major NTD groups. (*b*) Graphical representation of the three main groups of diseases according to parameters ε and φ: directly transmitted ($\varepsilon = 0$; $\varphi = 0$), environmentally transmitted, with focal transmission dependent on human prevalence ($\varepsilon = 1$; $\varphi = 0$) and environmentally transmitted, driven purely by exogenous environmental factors ($\varepsilon = 1$; $\varphi = 1$).

by definition $\varphi = 1$, while directly transmitted diseases have, by the nature of the close contact required for contagion, $\varphi \to 0$. For other parasites and pathogens, for example, those that experience intermediate levels of focal to exogenous transmission, the value of φ depends on the scale of analysis.

Figure 2 provides a simple qualitative description of common infective agents in tropical regions according to their transmission strategies based on parameters ε and φ. Many pathogens responsible for mortality in developing countries have low ε and φ, such as childhood diseases (measles and whooping cough), respiratory infections (tuberculosis) or sexually transmitted diseases (HIV and syphilis). By contrast, for most pathogens responsible for NTDs, environmental transmission plays an important role ($\varepsilon \to 1$). The general model described above, although difficult to parametrize in its simplest form [19,22], can be used to explore conceptual differences in dynamics and control strategies for a wide variety of pathogens and transmission strategies. A heuristic illustration of such insights is provided in figure 3, where we contrast the impact of common strategies of disease control for directly transmitted diseases ($\varepsilon = 0$, $\varphi = 0$) and ETDs ($\varepsilon = 1$, $\varphi \to 1$).

We show that for direct and ETDs with comparable basic reproduction numbers R_0 (i.e. number of secondary infections caused by an infected individual introduced in a susceptible population), control can be effectively achieved for directly transmitted disease through periodic medical treatment. All else being equal (i.e. in terms of the R_0 of the disease and the frequency and intensity of intervention), the same drug-focused strategies can have a reduced efficacy for diseases where the environmental reservoir plays an important role (figure 3*a*,*b*). In the latter case, more effective control can be achieved when classic treatment strategies are complemented with interventions that act on the environmental reservoir of the pathogen or reduce exposure (figure 3*c*). A detailed analysis of this system of equations, the parametrization for the presented simulations, and further explanations are provided in the electronic supplementary material, Appendix S1.

(b) Feedbacks between poverty and disease in coupled environment–human systems

Global patterns of poverty and disease have a strong geographic signature, indicative of underlying environmental determinants (figure 4) [26,27]. Building on recent advances in the modelling of coupled economic–epidemiological systems [11,28], we explore how the framework presented in §2a can be integrated with existing models of disease-driven poverty traps to understand the potential role of environmental drivers. This integrated framework is based on the intersection of the following empirical facts: (i) economic and environmental conditions are co-determinants of NTDs, and (ii) NTDs have well-documented negative effects on economic productivity, primarily through child development, educational attainment and labour productivity [1,27,29–31].

The effect of economic drivers on disease dynamics in a particular system can be captured by transforming some parameters in equations (2.1*a*,*b*) to be functions of *per capita* income or wealth: i.e. $\beta_D = \beta_D(k)$, $\beta_E = \beta_E(k)$, $\Omega = \Omega(k)$, $\lambda = \lambda(k)$; where k is capital, which we define broadly as a stock of economic resources used to produce income. For instance, transmission rates (β_D, β_E) and environmental recruitment of propagules (σ and Ω) are generally decreasing functions of capital k, because capital is necessary for prevention measures that reduce disease transmission, such as systems for water and sanitation, improved housing conditions or protective clothing [4,5,7]. In addition, the recovery rate $\gamma = \gamma(k)$ is generally an increasing function of capital because capital (or income generated from capital) is used for better nutrition and accessing healthcare [32,33]. The relationship of vectors $V = V(k)$ and the mortality rate of infective propagules $\delta = \delta(k)$ with capital (k, or economic development) are more context- and disease-specific [28].

The effects of disease on income can be captured by adding capital as a third state variable, in the tradition of economic

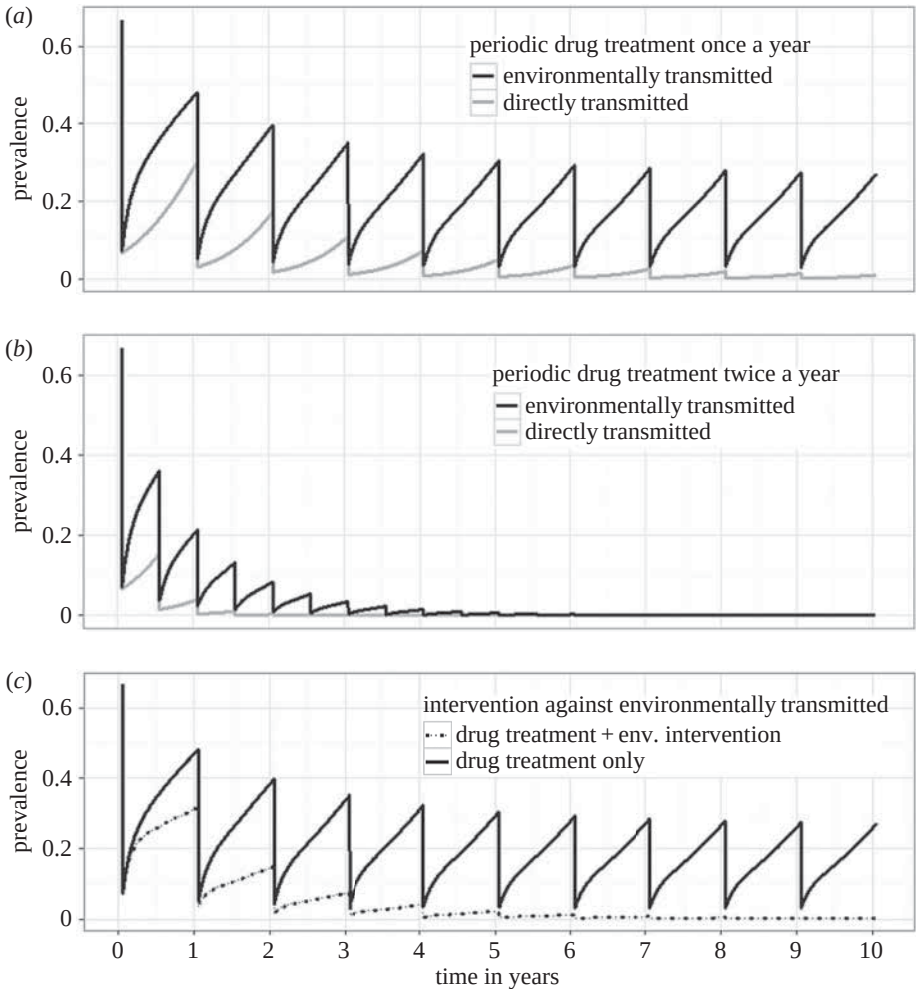

Figure 3. Effectiveness of periodic drug treatment and environmental interventions for the control of diseases with different transmission pathways. Population prevalence dynamics over 10 years for a directly transmitted disease (grey lines) and an ETD (black lines) with human drug treatment dispensed once a year (*a*) or twice a year (*b*). We considered a 90% drop in prevalence after each treatment and $R_0 = 3$ for both the directly transmitted and the ETD (see the electronic supplementary material, Appendix S1 for further parameter values). In (*c*), only the dynamics of an ETD are displayed, with model parameters set as in (*a*) and two interventions considered: only drug treatment administered once a year (solid line), and the same drug administration complemented with an environmental intervention (e.g. water sanitation, use of insecticide or biological control) that reduces life expectancy of the pathogen environmental stages by one-third (dashed line).

growth theory, to the infectious disease model [34,35]:

$$\frac{dk}{dt} = r(I)y(I,k) - dk, \tag{2.3}$$

where k is *per capita* physical or human capital; d is capital depreciation rate; r is capital accumulation or savings rate, which is negatively affected by disease I, and $y = y(I,k)$ is *per capita* income, an increasing function of capital and a decreasing function of disease prevalence in the population.

In coupled disease–economic systems [11,36,37], an increase in prevalence of either directly transmitted (electronic supplementary material, Appendix S1; $\varepsilon = 0$) or ETD (figure 5*a–c*; $\varepsilon = 1$) can trigger a sequence of cascading effects that reinforce conditions of poverty. Lower capital in turn fosters disease transmission (high β) and reduces recovery (low γ), ultimately creating a negative reinforcing cycle of poverty and disease. A substantial reduction in disease prevalence can trigger the opposite sequence of cascading effects, leading to a reinforcing cycle of better health, increased labour productivity and capital accumulation. Therefore, disease–economic systems can, under some circumstances, be characterized by bistability [11,36,37], where one locally stable equilibrium is associated with low income and high disease prevalence (i.e. a 'poverty trap') and the other equilibrium is characterized by high income and little or no disease (figure 5). The equilibrium outcome of either a poverty trap or a virtuous cycle towards health and productivity, is contingent on the history of the system and on specific 'shocks' in economic and/or healthcare investments that might push the disease–economic system from one basin of attraction to the other [36]. In the case of ETDs, such as most NTDs, disease–economic dynamics are highly influenced by the dynamics of the pathogen in the environment (figure 5*a–c*). As a result, the same strategies that could help break a disease-driven poverty trap for directly transmitted diseases, might not be sufficient for ETDs (figure 5*d–f*). Indeed, failure to act on the environmental reservoir, despite administration of periodic drug treatment, may prevent a sustained prevalence reduction under the critical threshold that switches the basin of attraction for ETDs, therefore perpetuating the poverty trap (figure 5*d–f*).

These models, which have not previously incorporated an environmental component of disease transmission, have been extended to include within-human population dynamics, where bistability can occur on coupled epidemiological/economic networks [34]. Even if diseases have low prevalence, and no bistability, disease–economic feedbacks can lead to

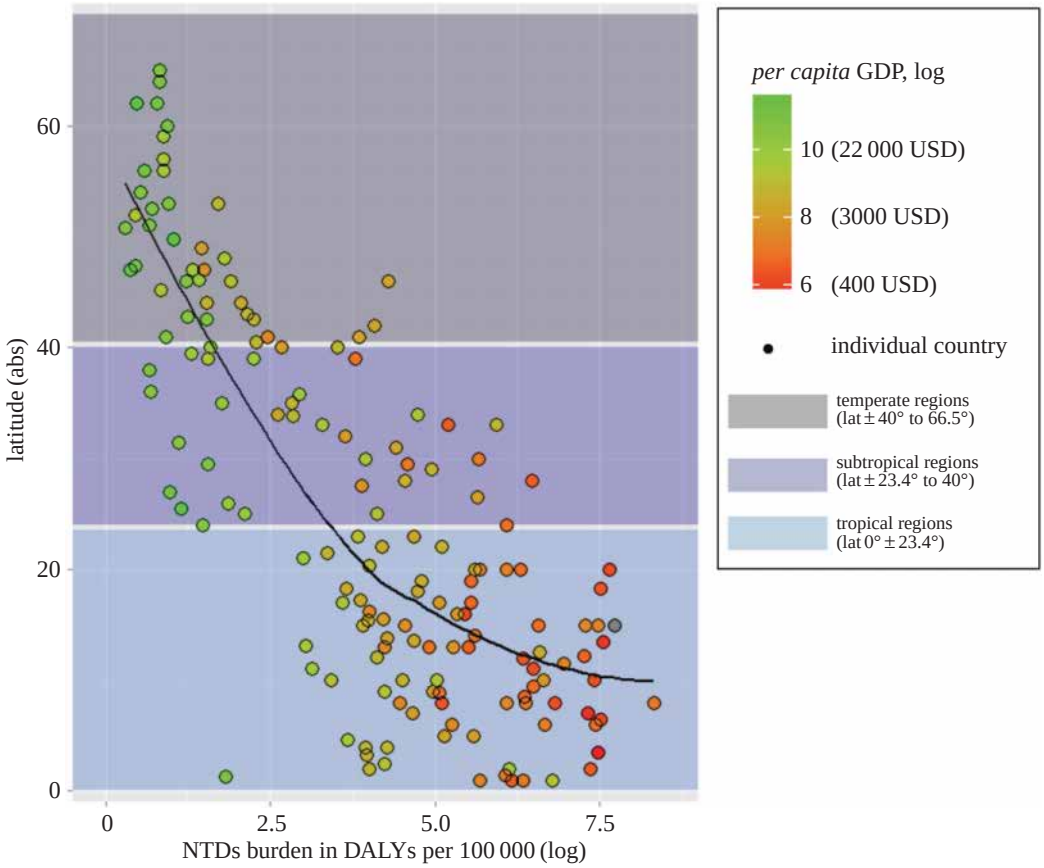

Figure 4. Latitudinal gradient in NTDs burden and poverty. Tropical and subtropical regions (blue and light blue shade) bear an overwhelming burden of NTDs, represented in the *x*-axis as DALY per 100 000 population (logarithmic scale). These regions accumulate 88.0% and 11.8% of the global number of NTD-related DALYs, respectively, which together represents more than 99% of the world burden. Concurrently, tropical and subtropical regions present some of the lowest levels of *per capita* GDP in the world (dot colour gradient from red for lowest GDP to green for highest GDP). The black solid line in the graph shows the relationship between latitude and NTD-related DALYs (loess nonlinear smoother). Figure was created with R statistical software (package ggplot2) with country data obtained from [23–25].

inequalities in cases of NTDs that cause lifelong disability [38]. Equations ((2.1)–(2.3)) therefore represent a simple modelling framework capable of accounting for a continuum of alternative infectious disease transmission pathways and socio-economic drivers that can be extended to account for system-specific contexts. To illustrate the concepts introduced in our framework for specific systems, we present in §§3 and 4, as case studies, recent evidence on socio-economic impacts, environmental drivers and ecological solutions for two NTDs with environmental transmission ($\varepsilon = 1$) at opposite extremes of the local-to-exogenous transmission (φ) axis in figure 2*a*. Buruli ulcer is a debilitating disease caused by a waterborne mycobacterium whose transmission to people depends on exogenous environmental reservoirs ($\varphi = 1$). Schistosomiasis is caused by a blood fluke, whose life cycle depends strongly on a transmission loop from infected people to the local aquatic environment (snails) and back to people ($\varphi = 0$ or close to zero).

3. Case study 1. Buruli ulcer: the need for ecological and socio-economic insights for disease control

Buruli ulcer, a devastating skin disease caused by the environmental pathogen *Mycobacterium ulcerans*, is probably one of the least-studied of all recognized NTDs. Discovered in the 1960s, it has rapidly emerged in tropical and subtropical countries and currently infects 5000 new people every year [39]. Most of the disease burden concentrates in rural areas of central and western Africa, where it presents a highly focal distribution, even within endemic regions [39]. Although initial stages of the disease (i.e. nodules, plaques and small ulcers) can be treated with an eight-week antibiotic regimen, poor access to healthcare in these areas frequently leads to catastrophic disease progression [40,41]. One in four cases experience functional limitations for life as a consequence of complications associated with the later stages of the disease (i.e. extensive ulcers, osteomyelitis) that require invasive surgery and lengthy hospital stays [40,41]. These pathological problems have socio-economic causes and consequences. Besides the enormous cost of the disease episode itself, estimated at 25% of household yearly income in Cameroon [42], handicap and deformity are associated with significant stigma, social isolation, job loss and school dropout [41,42]. Early detection and treatment of cases can avert much of the unnecessary suffering [3]. Yet, for ETDs like Buruli ulcer whose dynamics are driven by extrinsic environmental factors ($\varepsilon \to 1$, $\varphi \to 1$, figure 2), our poor understanding of the environmental mechanisms that drive pathogen ecological dynamics and its transmission to human populations undermines our capacity to prevent the disease.

Buruli ulcer is associated with aquatic ecosystems, and *M. ulcerans* is found in water, mud, aquatic plants and freshwater insects from representative taxa of the whole aquatic community [43]. The ubiquity of this multi-host environmentally persistent pathogen is exacerbated by the lack of safe water in endemic rural areas, where daily activities, such as bathing or washing, repeatedly expose people to infection

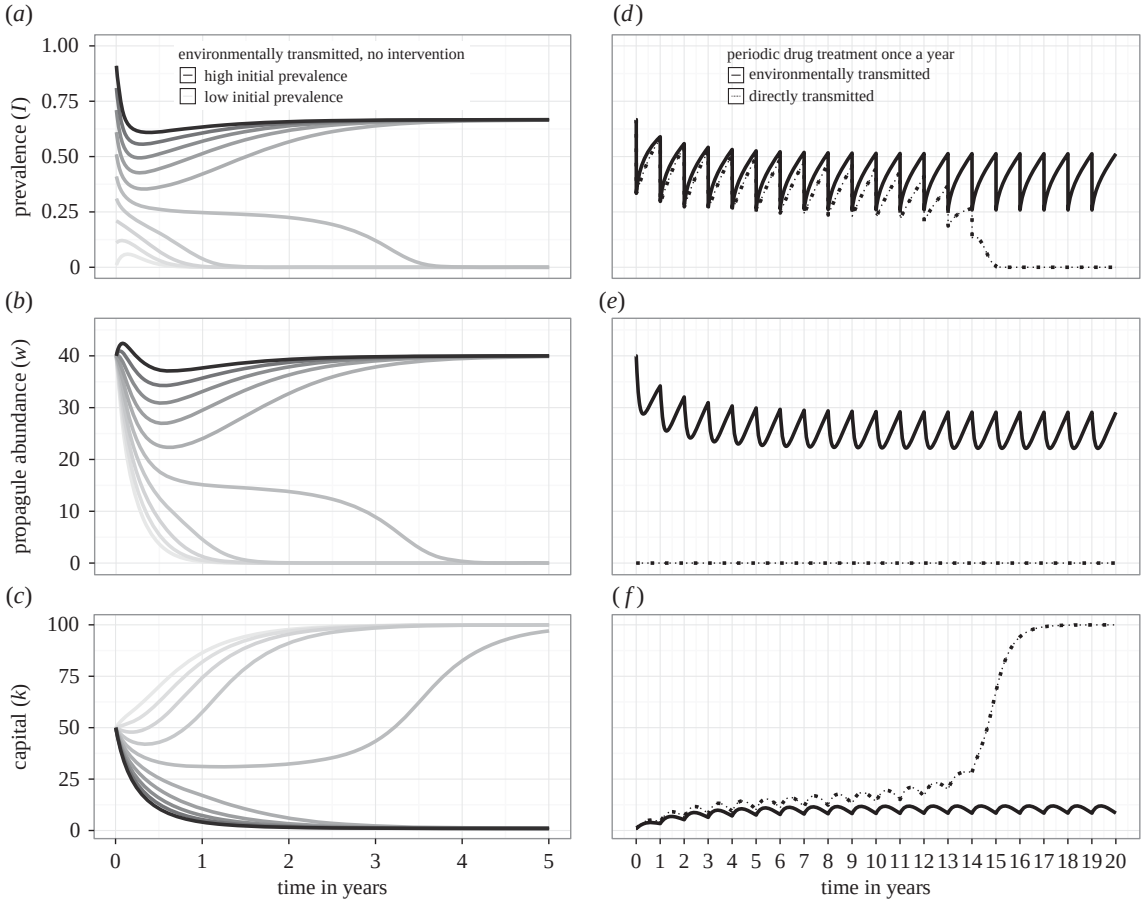

Figure 5. Dynamics of coupled economic–epidemiological systems and impact of periodic drug treatment for directly and environmentally transmitted diseases. Graphs are based on the coupled system described in the main text, and parameter values described in the electronic supplementary material, Appendix S1. (*a–c*) Dynamics over 5 years in a coupled system for the case of an ETD with $R_0 = 3$. Graphs display dynamics of human prevalence (*I*), pathogen environmental abundance (*W*), and *per capita* capital (*k*), starting from a range of initial conditions for prevalence *I*, with same *k* and *W*. Shades are increasingly dark for increasing values of initial prevalence. Bistability emerges from this system, with two equilibria depending on initial conditions: a high prevalence low capital equilibrium, and a low prevalence high capital equilibrium. (*d–f*) Impact of human drug treatment dispensed once a year on the dynamics over 20 years for a directly transmitted disease (dotted lines) and an ETD (solid lines) in a coupled economic–epidemiological system. Initial conditions were set as in the high-prevalence–low-capital equilibrium in the left panel, to assess the effectiveness of this intervention to break a theoretical disease-driven poverty trap. $R_0 = 3$ for both types of disease.

[44,45]. Prevalence of the disease is concentrated near swamps, flooded areas and along the basin of slow-flowing rivers at low elevation. Land-use change due to agricultural practices, deforestation, or the construction of dams and roads have been correlated with the emergence of Buruli ulcer endemic areas [43]. Recent advances in disease ecology are shedding light on the conditions that favour environmental persistence and growth of *M. ulcerans*, and drive its spatio-temporal dynamics (*W* in equation (2.1*b*)). *M. ulcerans* thrives in periods of intensive rainfall, and certain physicochemical conditions of lentic ecosystems (i.e. low water flow, low oxygen, mildly acidic pH, high temperature) may allow persistence as free-living stages [46,47] (figure 6*a*). Under unfavourable water conditions, trophic transmission between aquatic hosts seems to ensure the presence of *M. ulcerans* in the environment, independently of the infections in people, which may explain the ubiquity of the pathogen in endemic regions [46,47].

An ecological perspective can also provide new insights on Buruli ulcer transmission. It is unclear whether direct entry into the skin [43] or vector transmission through the bites of water bugs [49] are major contributors to transmission. Ecological studies recently provided the first field-based evidence that environmental transmission to humans could play a greater role than vector transmission (figure 6*b*) and suggested that *M. ulcerans*' environmental load could predict the temporal and spatial patterns of Buruli ulcer incidence [48]. Integration of this ecological understanding with known socio-economic features of the disease in coupled economic–epidemiological models (as shown in equations (2.1)–(2.3)) is helping to clarify the economic consequences of land-use change through their effects on Buruli ulcer [38]. These models show that in contexts of high environmental risk, Buruli ulcer can cause economic inequalities at the population level (figure 6*c*), with disproportionate impacts on the poorest socio-economic groups due to disparities in vulnerability and healthcare access [38]. Thus, the negative consequences of land-use change could fall disproportionally on the poor. These studies represent an initial step towards a more comprehensive understanding of Buruli ulcer environmental risk, transmission and economics that could lead to the implementation of novel control strategies.

4. Case study 2. Schistosomiasis: an ecological solution for disease control and economic development

Schistosomiasis is a debilitating disease caused by freshwater trematodes of the genus *Schistosoma* and one of the most

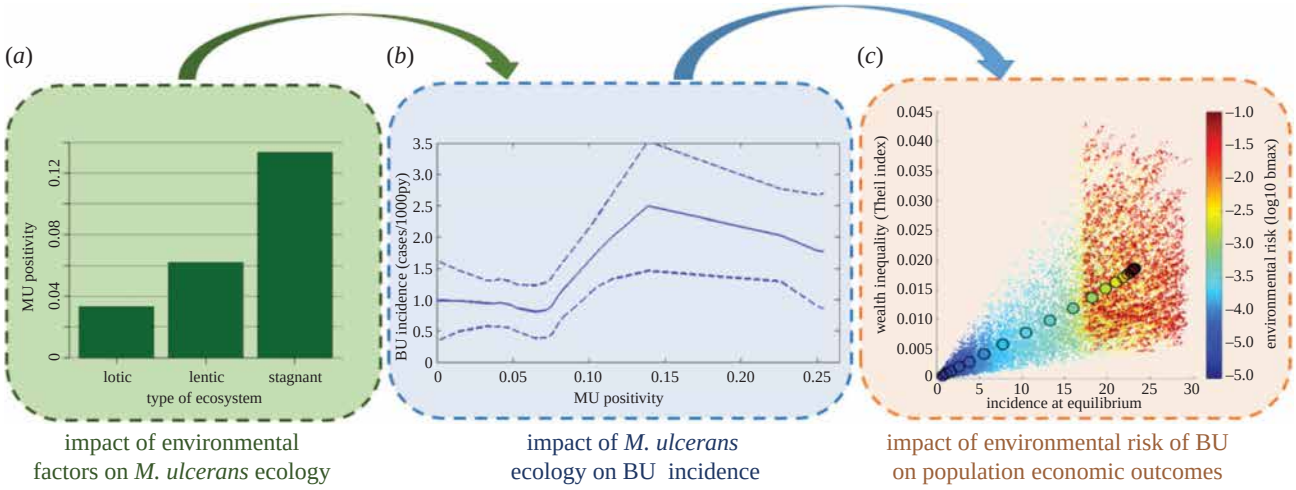

Figure 6. Understanding feedbacks between environment, Buruli ulcer and economic development. A recent research initiative in Cameroon sought to characterize the environmental dynamics of *M. ulcerans* through frequent sampling of multiple aquatic ecosystems and molecular analyses, in order to gain new insights on the ecology and epidemiology of the disease. (*a*) The prevalence of the bacteria in aquatic sites (MU positivity) appeared to be favoured by specific conditions in stagnant and slow-flowing (lentic) ecosystems [46]. (*b*) Comparisons of *M. ulcerans* ecological dynamics with patterns of Buruli ulcer incidence from the same areas in mathematical and statistical models, showed that spatial and temporal patterns of Buruli ulcer (*y*-axis) were influenced by the environmental prevalence of *M. ulcerans* (*x*-axis) [48]. (*c*) Individual-based model simulations of a coupled economic–epidemiological system adapted to Buruli ulcer revealed that the disease can be responsible of economic inequalities in endemic populations, with increases in Theil index (*y*-axis) as a function of BU incidence (*x*-axis) and *M. ulcerans* environmental load (colour gradient) [38]. Figures are adapted from Garchitorena *et al*. [38,46,48].

important NTDs based on number of people at risk (almost 800 million) and number infected (approximately 250 million) [3,4,50,51]. More than 90% of infections occur in sub-Saharan Africa, the vast majority of which occur in school-aged children between 5 and 15 years old [5]. Infection occurs through exposure to natural freshwater ecosystems in tropical areas that are inhabited by obligate intermediate hosts of the parasites—snails of the genus *Bulinus* and *Biomphalaria*. The snails become infected when people (or, in some case other vertebrate hosts such as rodents or cattle) shed parasite eggs into the environment through urine or faeces ($\varepsilon \to 1$, $\varphi \to 0$, figure 2). People (or other vertebrate hosts) are infected when they come into contact with waters containing infectious larvae shed from snails. As with Buruli ulcer, exposure commonly occurs through bathing, washing dishes, fishing or other water-based daily activities. Infection with *Schistosoma* spp. can trigger acute and chronic inflammatory processes such as haematuria, scarring, calcification, squamous cell carcinoma and occasional embolic egg granulomas in brain or spinal cord (*S. japonicum*) as well as fever, hepatic egg granulomas, fibrosis and portal hypertension (*S. mansonii*) [52]. Inflammatory processes lead to debilitation, stunted growth and cognitive impairment in children, increased chances of acquiring HIV in the case of urogenital schistosomiasis in women, and may eventually lead to liver, lung or kidney failure. The drug of choice for schistosomiasis, praziquantel, is cheap (US $0.32 to treat a child [53]) and effective in removing parasites from infected people [52,53]. Yet, despite more than US $1.4 billion spent in the past two decades on MDA programmes in developing countries, prevalence and intensity of infection have changed little compared with the pre-praziquantel era [54]. This is because, after treatment, rural villagers have few alternatives but to return to the parasite-contaminated waters (figure 3), and parasitic loads in people return to pre-treatment levels in as little as six months [55,56].

In Africa, the development of irrigation systems and the construction of dams often lead to a further expansion of the habitat of snails (an increase in parameter V in equation (2.1*b*)), and hence new potential transmission sites for schistosomiasis [57,58]. The construction of the Diama Dam, built at the mouth of the Senegal River in 1986, is a textbook case. Urinary schistosomiasis was endemic at very low levels before the construction of the dam and intestinal schistosomiasis was absent. The first new cases of both intestinal and urinary schistosomiasis were reported about 1 year after the completion of the Diama Dam [59]. Following two decades of exponential growth in the number of infected people, the lower basin of the Senegal River has now become a hyper-endemic region for schistosomiasis [59]. The construction of the Diama Dam not only led to an expansion of good snail habitat—i.e. a year-around stable water body at low salinity—but also decimated populations of the migratory prawn, *Macrobrachium vollenhovenii*, a voracious predator of snails [58,60,61]. The combination of increased habitat for the snail population with the removal of a very effective predator provided ideal environmental conditions for *Bulinus* and *Biomphalaria* snails to thrive and amplify schistosomiasis transmission.

A pilot study carried out in 2011–2014 provided supportive evidence that the reintroduction of the freshwater prawn can reduce infected snails and significantly lower reinfection rates in the human population [56]. Computer simulations showed that the combination of MDA and prawn reintroduction can achieve results that neither of these approaches can attain independently [56]. As prawns are a delicious food commodity with market value, the development of prawn production through aquaculture could also alleviate hunger and provide a source of revenue for local villagers, so that prawn restoration could become an actionable ecological solution leading to a mutually beneficial outcome for biodiversity, schistosomiasis reduction, food production and income [56]. An extended analysis of the geographical distribution of dams and 24 marketable prawn species around the world in areas where schistosomiasis is endemic [58] shows that the removal of natural predators of schistosomiasis-bearing snails might have occurred in many other places in addition

to Senegal. The reintroduction of these predators, either through ecological restoration or aquaculture, might protect people from the risk of contracting schistosomiasis and could complement drug-distribution programmes [58].

5. Discussion and Conclusion

While poverty, infectious disease, and environmental change have been the subject of much independent investigation, they are interlinked in complex ways that require integrated study in order to meet key targets in the Sustainable Development Goals [9]. Poverty and weak health systems arguably pose the most important risk factors for acquiring and succumbing to infectious diseases. Less recognized is the fact that pathogens and parasites responsible for most tropical diseases of poverty are predominantly transmitted through environmental pathways and highly influenced by ecological factors. Here, we describe a simple framework for studying the complex relationships between poverty, infectious diseases, and the environment. The aim of this framework is to help investigate environmental drivers of joint poverty–disease dynamics, with the ultimate goal of identifying sustainable solutions for human and planetary health. Preliminary analyses illustrate the limited effectiveness of human drug treatment for the control of ETDs, when compared with directly transmitted diseases. Although the model cannot be realistically parametrized for specific diseases in its simplest form, this key conceptual difference highlights opportunities for environmental interventions for disease control. By integrating ecological dynamics into coupled disease–economic systems, we show that the presence of persistent environmental reservoirs of pathogens may affect both NTD prevalence and poverty. Future research is needed to investigate how interrupting environmental transmission cycles [3,7] can complement current efforts to expand preventive and curative services for the poorest groups [62,63] to break cycles of poverty and disease.

Building on current ecological knowledge, cost-effective interventions for disease prevention can be designed for many infectious diseases of poverty [64–66]. Mosquito control strategies are among the most widely recognized and extensively deployed of these interventions [67]. In the absence of an effective vaccine for malaria and caution against drug resistance, the recent reduction in disease burden in sub-Saharan Africa has been largely driven by the massive scale-up of indoor residual spraying and long-lasting insecticidal nets [67]. Other examples can be found for zoonotic diseases such as Nipah virus, where the use of bamboo skirts provides a physical barrier that prevents bats (the natural reservoir of NiV) from accessing date palm sap, subsequently reducing transmission to human populations [68,69]. The integration of drug administration with basic infrastructure investments in water, sanitation and hygiene (WASH) has been recognized as a priority in the prevention and care for multiple NTDs, along with improved living conditions, integrated vector control, health education and stronger health systems in endemic areas [3,70]. Yet, the immediate investment costs of infrastructure development hinder the implementation of WASH and similar interventions, leaving drug treatment as the main control strategy for most NTDs. For sapronoses, whose presence in the environment is independent of human infections, such as fungal and waterborne bacterial infections (e.g. Buruli ulcer), more research on environmental drivers will help identify transmission hot spots, contribute to early detection of cases, and inform prevention strategies [46,48]. For ETDs with well-known ecological drivers, such as trematode and vector-borne infections (e.g. schistosomiasis), control strategies based on natural enemies of pathogens or their wildlife hosts/vectors could represent sustainable ecological solutions. A recent analysis of a century of schistosomiasis control programmes [54] showed that, before the availability of the anti-parasitic drug praziquantel, successful elimination was achieved via interventions that directly targeted the snail intermediate host [54,71]. Supportive evidence [56,58,60] suggests that freshwater prawns may reduce disease transmission through predation on schistosomiasis-bearing snails. More research is needed to identify what other natural enemies of parasites or of their wildlife hosts could be successfully harnessed to achieve a better control of disease transmission [72,73]. While broadly used for integrated pest control in agriculture, such ecological strategies have received little attention in the literature of human infectious diseases. Despite showing promising results in the fight against malaria and other vector-borne diseases, environmental strategies to complement medical approaches still remain poorly developed and under recognized [74].

The many dimensions of the Sustainable Development Goals and an increased attention to the interdependence of human wellbeing and the Earth's provisioning of ecosystem services, have recently expanded the focus of the global health community into the new scientific movement of Planetary Health [9]. While this movement reflects a wide consensus on the threats and challenges currently faced by human populations and natural systems, we still lack actionable solutions that cost-effectively leverage our understanding of the ecology of disease transmission to break the reinforcing cycles of poverty, environmental change and disease. To make the Planetary Health concept actionable, research efforts can help identify specific keystone systems for developing and deploying ecological interventions that influence both poverty and disease.

Authors' contributions. A.G., S.H.S., M.H.B. and G.D.L. conceived the study. G.D.L. analysed the model. All authors helped draft the manuscript and gave final approval for publication.

Competing interests. The authors declare no competing financial interests.

Funding. S.H.S. and G.D.L. have been supported by NSF CNH grant no. 1414102, the Bill and Melinda Gates Foundation, NIH grant no. 1R01TW010286-01, Stanford GDP SEED grant no. 1183573-100-GDPAO, the SNAP-NCEAS-supported working group 'Ecological levers for health: Advancing a priority agenda for Disease Ecology and Planetary Health in the 21st century' and the NIMBioS-supported working group on the Optimal Control of ETDs. A.G., C.N.N. and M.H.B. were funded by a James McDonnell Foundation grant (no. 220020322) and NIH grant (no. K01TW008773) from the Fogarty International Center. This work was partly supported by the National Center for Ecological Analysis and Synthesis (NCEAS) and the National Socio-Environmental Synthesis Center (SESYNC) with funds from the NSF. J.F.G. and B.R. were supported by a French grant from the Agence Nationale de la Recherche (CEBA ANR-LABX-10-2501) and J.F.G. received support from the UN programme FutureEarth. E.A.M. was supported by grants from the NSF (DEB-1518681 and DEB-1640780), a Stanford Center for Innovation in Global Health seed grant, and a Stanford Woods Institute Environmental Ventures Program grant.

Acknowledgements. We are grateful to Alain Rasolomampiandra for creating the artwork in figures 1 and 2.

References

1. Sachs J. 2001 Macroeconomics and health: investing in health for economic development. Report of the Commission on Macroeconomics and Health. Geneva, Switzerland: WHO.
2. Lozano R *et al.* 2012 Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**, 2095–2128. (doi:10.1016/S0140-6736(12)61728-0)
3. World Health Organization 2015 Investing to overcome the global impact of neglected tropical diseases: Third WHO report on neglected tropical diseases. Geneva, Switzerland: WHO.
4. Hotez PJ, Fenwick A, Savioli L, Molyneux DH. 2009 Rescuing the bottom billion through control of neglected tropical diseases. *Lancet* **373**, 1570–1575. (doi:10.1016/S0140-6736(09)60233-6)
5. Hotez PJ, Kamath A. 2009 Neglected tropical diseases in sub-Saharan Africa: review of their prevalence, distribution, and disease burden. *PLoS Negl. Trop. Dis.* **3**, e412. (doi:10.1371/journal.pntd.0000412)
6. Fenwick A. 2012 The global burden of neglected tropical diseases. *Public Health* **126**, 233–236. (doi:10.1016/j.puhe.2011.11.015)
7. IOM (Institute of Medicine) 2011 *The causes and impacts of neglected tropical and zoonotic diseases: opportunities for integrated intervention strategies*. Washington, DC: National Academies Press.
8. Webster JP, Molyneux DH, Hotez PJ, Fenwick A. 2014 The contribution of mass drug administration to global health: past, present and future. *Phil. Trans. R. Soc. B* **369**, 1–12. (doi:10.1098/rstb.2013.0434)
9. Whitmee S *et al.* 2015 Safeguarding human health in the anthropocene epoch: report of the Rockefeller Foundation-Lancet commission on planetary health. *Lancet* **386**, 1973–2028. (doi:10.1016/S0140-6736(15)60901-1)
10. Kuris AM, Lafferty KD, Sokolow SH. 2014 Sapronosis: a distinctive type of infectious agent. *Trends Parasitol.* **30**, 386–393. (doi:10.1016/j.pt.2014.06.006)
11. Ngonghala CN, Plucíński MM, Murray MB, Farmer PE, Barrett CB, Keenan DC, Bonds MH. 2014 Poverty, disease, and the ecology of complex systems. *PLoS Biol.* **12**, e1001827. (doi:10.1371/journal.pbio.1001827)
12. Barrett CB, Travis AJ, Dasgupta P. 2011 On biodiversity conservation and poverty traps. *Proc. Natl Acad. Sci. USA* **108**, 13 907–13 912. (doi:10.1073/pnas.1011521108)
13. Guernier V, Hochberg ME, Guégan J-F. 2004 Ecology drives the worldwide distribution of human diseases. *PLoS Biol.* **2**, e141. (doi:10.1371/journal.pbio.0020141)
14. Dunn RR, Davies TJ, Harris NC, Gavin MC. 2010 Global drivers of human pathogen richness and prevalence. *Proc. R. Soc. B* **277**, 2587–2595. (doi:10.1098/rspb.2010.0340)
15. Ostfeld RS, Keesing F, Eviner VT. 2008 *Infectious disease ecology: effects of ecosystems on disease and of disease on ecosystems*. Princeton, NJ: Princeton University Press.
16. Githeko AK, Lindsay SW, Confalonieri UE, Patz JA. 2000 Climate change and vector-borne diseases: a regional analysis. *Bull. World Health Organ.* **78**, 1136–1147.
17. Keesing F *et al.* 2010 Impacts of biodiversity on the emergence and transmission of infectious diseases. *Nature* **468**, 647–652. (doi:10.1038/nature09575)
18. Civitello DJ *et al.* 2015 Biodiversity inhibits parasites: broad evidence for the dilution effect. *Proc. Natl Acad. Sci. USA* **112**, 8667–8671. (doi:10.1073/pnas.1506279112)
19. Eisenberg MC, Robertson SL, Tien JH. 2013 Identifiability and estimation of multiple transmission pathways in cholera and waterborne disease. *J. Theor. Biol.* **324**, 84–102. (doi:10.1016/j.jtbi.2012.12.021)
20. Codeço CT. 2001 Endemic and epidemic dynamics of cholera: the role of the aquatic reservoir. *BMC Infect. Dis.* **1**, 1. (doi:10.1186/1471-2334-1-1)
21. Tien JH, Earn DJD. 2010 Multiple transmission pathways and disease dynamics in a waterborne pathogen model. *Bull. Math. Biol.* **72**, 1506–1533. (doi:10.1007/s11538-010-9507-6)
22. Eisenberg JNS, Desai MA, Levy K, Bates SJ, Liang S, Naumoff K, Scott JC. 2007 Environmental determinants of infectious disease: a framework for tracking causal links and guiding public health research. *Environ. Health Perspect.* **115**, 1216–1223. (doi:10.1289/ehp.9806)
23. Institute for Health Metrics and Evaluation 2016 GDB results tool. Seattle, WA: IHME, University of Washington. See http://ghdx.healthdata.org/gbd-results-tool.
24. World Bank 2015 World Bank Open Data. See http://data.worldbank.org/.
25. US Central Intelligence Agency 2016 *The world factbook*. See https://www.cia.gov/library/publications/the-world-factbook.
26. Sachs JD. 2001 Tropical underdevelopment. *NBER Work. Pap.* 8119. Cambridge, MA: National Bureau of Economic Research. (doi:10.3386/w8119)
27. Bonds MH, Dobson AP, Keenan DC. 2012 Disease ecology, biodiversity, and the latitudinal gradient in income. *PLoS Biol.* **10**, e1001456. (doi:10.1371/journal.pbio.1001456)
28. Baeza A, Bouma MJ, Dhiman RC, Baskerville EB, Ceccato P, Yadav RS, Pascual M. 2013 Long-lasting transition toward sustainable elimination of desert malaria under irrigation development. *Proc. Natl Acad. Sci. USA* **110**, 15 157–15 162. (doi:10.1073/pnas.1305728110)
29. Miguel E, Kremer M. 2004 Worms: identifying impacts on education and health in the presence of treatment externalities. *Econometrica* **72**, 159–217. (doi:10.1111/j.1468-0262.2004.00481.x)
30. Sachs J, Malaney P. 2002 The economic and social burden of malaria. *Nature* **415**, 680–685. (doi:10.1038/415680a)
31. Nokes C, Grantham-McGregor SM, Sawyer AW, Cooper ES, Bundy DA. 1992 Parasitic helminth infection and cognitive function in school children. *Proc. R. Soc. Lond. B* **247**, 77–81. (doi:10.1098/rspb.1992.0011)
32. Makinen M *et al.* 2000 Inequalities in health care use and expenditures: empirical data from eight developing countries and countries in transition. *Bull. World Health Organ.* **78**, 55–65.
33. Whitehead M, Dahlgren G, Evans T. 2001 Equity and health sector reforms: can low-income countries escape the medical poverty trap? *Lancet* **358**, 833–836. (doi:10.1016/S0140-6736(01)05975-X)
34. Solow RM. 1956 A. contribution to the theory of economic growth. *Q. J. Econ.* **70**, 65–94. (doi:10.2307/1884513)
35. Barro RJ, Sala-i-Martin X. 2004 *Economic growth*. Cambridge, MA: MIT Press.
36. Bonds MH, Keenan DC, Rohani P, Sachs JD. 2010 Poverty trap formed by the ecology of infectious diseases. *Proc. R. Soc. B* **277**, 1185–1192. (doi:10.1098/rspb.2009.1778)
37. Plucíński MM, Ngonghala CN, Getz WM, Bonds MH. 2013 Clusters of poverty and disease emerge from feedbacks on an epidemiological network. *J. R. Soc. Interface* **10**, 20120656. (doi:10.1098/rsif.2012.0656)
38. Garchitorena A, Ngonghala CN, Guegan J-F, Texier G, Bellanger M, Bonds M, Roche B. 2015 Economic inequality caused by feedbacks between poverty and the dynamics of a rare tropical disease: the case of Buruli ulcer in sub-Saharan Africa. *Proc. R. Soc. B* **282**, 20151426. (doi:10.1098/rspb.2015.1426)
39. Johnson PDR, Stinear T, Small PLC, Pluschke G, Merritt RW, Portaels F, Huygen K, Hayman JA, Asiedu K. 2005 Buruli ulcer (*M. ulcerans* infection): new insights, new hope for disease control. *PLoS Med.* **2**, e108. (doi:10.1371/journal.pmed.0020108)
40. Barogui Y, Johnson RC, van der Werf TS, Sopoh G, Dossou A, Dijkstra PU, Stienstra Y. 2009 Functional limitations after surgical or antibiotic treatment for Buruli ulcer in Benin. *Am. J. Trop. Med. Hyg.* **81**, 82–87.
41. Stienstra Y *et al.* 2005 Factors associated with functional limitations and subsequent employment or schooling in Buruli ulcer patients. *Trop. Med. Int. Heal.* **10**, 1251–1257. (doi:10.1111/j.1365-3156.2005.01519.x)
42. Grietens KP, Boock AU, Peeters H, Hausmann-Muela S, Toomer E, Ribera JM. 2008 'It is me who endures but my family that suffers': social isolation as a consequence of the household cost burden of Buruli ulcer free of charge hospital treatment. *PLoS Negl. Trop. Dis.* **2**, e321. (doi:10.1371/journal.pntd.0000321)
43. Merritt RW, Walker ED, Small PLC, Wallace JR, Johnson PDR, Benbow ME, Boakye DA. 2010 Ecology and transmission of Buruli ulcer disease: a systematic review. *PLoS Negl. Trop. Dis.* **4**, e911. (doi:10.1371/journal.pntd.0000911)
44. Debacker M, Portaels F, Aguiar J, Steunou C, Zinsou C, Meyers W, Dramaix M. 2006 Risk factors for Buruli ulcer, Benin. *Emerg. Infect. Dis.* **12**, 1325–1331. (doi:10.3201/eid1209.050598)

45. Nackers F, Johnson RC, Glynn JR, Zinsou C, Tonglet R, Portaels F. 2007 Environmental and health-related risk factors for *Mycobacterium ulcerans* disease (*Buruli ulcer*) in Benin. *Am. J. Trop. Med. Hyg.* **77**, 834–836.
46. Garchitorena A, Guégan J-F, Léger L, Eyangoh S, Marsollier L, Roche B. 2015 *Mycobacterium ulcerans* dynamics in aquatic ecosystems are driven by a complex interplay of abiotic and biotic factors. *Elife* **4**, 1–19. (doi:10.7554/eLife.07616)
47. Garchitorena A *et al.* 2014 *Mycobacterium ulcerans* ecological dynamics and its association with freshwater ecosystems and aquatic communities: results from a 12-month environmental survey in Cameroon. *PLoS Negl. Trop. Dis.* **8**, e2879. (doi:10.1371/journal.pntd.0002879)
48. Garchitorena A, Ngonghala CN, Texier G, Landier J, Eyangoh S, Bonds MH, Guégan J-F, Roche B. 2015 Environmental transmission of *Mycobacterium ulcerans* drives dynamics of Buruli ulcer in endemic regions of Cameroon. *Nat. Sci. Reports* **5**, 18055. (doi:10.1038/srep18055)
49. Marsollier L *et al.* 2002 Aquatic insects as a vector for *Mycobacterium ulcerans*. *Appl. Environ. Microbiol.* **68**, 4623–4628. (doi:10.1128/AEM.68.9.4623)
50. Lai Y *et al.* 2015 Spatial distribution of schistosomiasis and treatment needs in sub-Saharan Africa: a systematic review and geostatistical analysis. *Lancet. Infect. Dis.* **3099**, 1–14. (doi:10.1016/S1473-3099(15)00066-3)
51. Hotez PJ *et al.* 2014 The global burden of disease study 2010: interpretation and implications for the neglected tropical diseases. *PLoS Negl. Trop. Dis.* **8**, e0002865. (doi:10.1371/journal.pntd.0002865)
52. Ross AGP, Bartley PB, Sleigh AC, Olds GR, Li Y, Williams GM, McManus DP. 2002 Schistosomiasis. *N. Engl. J. Med.* **346**, 1212–1220. (doi:10.1056/NEJMra012396)
53. Hotez PJ, Fenwick A, Kjetland EF. 2009 Africa's 32 cents solution for HIV/AIDS. *PLoS Negl. Trop. Dis.* **3**, e430. (doi:10.1371/journal.pntd.0000430)
54. Sokolow S *et al.* 2016 Global assessment of schistosomiasis control over the past century shows targeting the snail intermediate host works best. *PLoS Negl. Trop. Dis.* **7**, e0004794. (doi:10.1371/journal.pntd.0004794)
55. Webster BL, Diaw OT, Seye MM, Faye DS, Stothard JR, Sousa-Figueiredo JC, Rollinson D. 2013 Praziquantel treatment of school children from single and mixed infection foci of intestinal and urogenital schistosomiasis along the Senegal River Basin: monitoring treatment success and re-infection patterns. *Acta Trop.* **128**, 292–302. (doi:10.1016/j.actatropica.2012.09.010)
56. Sokolow SH *et al.* 2015 Reduced transmission of human schistosomiasis after restoration of a native river prawn that preys on the snail intermediate host. *Proc. Natl Acad. Sci. USA* **112**, 9650–9655. (doi:10.1073/pnas.1502651112)
57. Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J. 2006 Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. *Lancet Infect. Dis.* **6**, 411–425. (doi:10.1016/S1473-3099(06)70521-7)
58. Sokolow SH *et al.* 2017 Nearly 400 million people are at higher risk of schistosomiasis because dams block the migration of snail-eating river prawns. *Phil. Trans. R. Soc. B* **372**, 20160127. (doi:10.1098/rstb.2016.0127)
59. Sow S, de Vlas SJ, Engels D, Gryseels B. 2002 Water-related disease patterns before and after the construction of the Diama dam in northern Senegal. *Ann. Trop. Med. Parasitol.* **96**, 575–586. (doi:10.1179/000349802125001636)
60. Sokolow SH, Lafferty KD, Kuris AM. 2014 Regulation of laboratory populations of snails (*Biomphalaria* and *Bulinus* spp.) by river prawns, *Macrobrachium* spp. (Decapoda, Palaemonidae): implications for control of schistosomiasis. *Acta Trop.* **132**, 64–74. (doi:10.1016/j.actatropica.2013.12.013)
61. Swartz SJ, De Leo GA, Wood CL, Sokolow SH. 2015 Infection with schistosome parasites in snails leads to increased predation by prawns: implications for human schistosomiasis control. *J. Exp. Biol.* **218**, 3962–3967. (doi:10.1242/jeb.129221)
62. Kim JY, Farmer PE, Porter ME. 2013 Redefining global health-care delivery. *Lancet* **382**, 1060–1069. (doi:10.1016/S0140-6736(13)61047-8)
63. Sachs JD. 2012 Achieving universal health coverage in low-income settings. *Lancet* **380**, 944–947. (doi:10.1016/S0140-6736(12)61149-0)
64. Prüss-Üstün A, Corvalán C. 2007 How much disease burden can be prevented by environmental interventions? *Epidemiology* **18**, 167–178. (doi:10.1097/01.ede.0000239647.26389.80)
65. Kilpatrick AM, Salkeld DJ, Titcomb G, Hahn MB. 2017 Conservation of biodiversity as a strategy for improving human health and well-being. *Phil. Trans. R. Soc. B* **372**, 20160131. (doi:10.1098/rstb.2016.0131)
66. Pattanayak SK, Kramer RA, Vincent JR. 2017 Ecosystem change and human health: implementation economics and policy. *Phil. Trans. R. Soc. B* **372**, 20160130. (doi:10.1098/rstb.2016.0130)
67. World Health Organization 2014 World malaria report 2013. Geneva, Switzerland: WHO.
68. Khan SU, Gurley ES, Hossain MJ, Nahar N, Sharker MAY, Luby SP. 2012 A randomized controlled trial of interventions to impede date palm sap contamination by bats to prevent Nipah virus transmission in Bangladesh. *PLoS ONE* **7**, 1–7. (doi:10.1371/journal.pone.0042689)
69. Islam MS *et al.* 2016 Nipah virus transmission from bats to humans associated with drinking traditional liquor made from date palm sap, Bangladesh, 2011–2014. *Emerg. Infect. Dis.* **22**, 664–670. (doi:10.3201/eid2204.151747)
70. World Health Organisation 2015 *Water sanitation & hygiene for accelerating and sustaining progress on neglected tropical diseases 2015–2020*. Geneva, Switzerland: WHO.
71. Pointier JP, Theron A, Imbert-Establet D. 1989 Decline of a sylvatic focus of *Schistosoma mansoni* in Guadeloupe (French West Indies) following the competitive displacement of the snail host *Biomphalaria glabrata* by *Ampullaria glauca*. *Oecologia* **75**, 38–43. (doi:10.1007/BF00378811)
72. Wu T, Perrings C. 2017 Conservation, development and the management of infectious disease: avian influenza in China, 2004–2012. *Phil. Trans. R. Soc. B* **372**, 20160126. (doi:10.1098/rstb.2016.0126)
73. Young HS *et al.* 2017 Interacting effects of land use and climate on rodent-borne pathogens in central Kenya. *Phil. Trans. R. Soc. B* **372**, 20160116. (doi:10.1098/rstb.2016.0116)
74. Kamareddine L. 2012 The biological control of the malaria vector. *Toxins* (*Basel*) **4**, 748–767. (doi:10.3390/toxins4090748)

PLOS MEDICINE

RESEARCH ARTICLE

Assessing trends in the content of maternal and child care following a health system strengthening initiative in rural Madagascar: A longitudinal cohort study

Camille Ezran[1]*, Matthew H. Bonds[2,3], Ann C. Miller[3], Laura F. Cordier[2], Justin Haruna[2], David Mwanawabenea[2], Marius Randriamanambintsoa[4], Hery-Tiana R. Razanadrakato[4], Mohammed Ali Ouenzar[2], Bénédicte R. Razafinjato[2], Megan Murray[3], Andres Garchitorena[2,5]*

1 Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California, United States of America, **2** PIVOT, Ranomafana, Madagascar, **3** Department of Global Health and Social Medicine, Harvard Medical School, Blavatnik Institute, Boston, Massachusetts, United States of America, **4** Direction de la Démographie et des Statistiques Sociales, Institut National de la Statistique, Antananarivo, Madagascar, **5** MIVEGEC, Univ Montpellier, CNRS, IRD, Montpellier, France

* camillee@stanford.edu (CE); andres.garchitorena@gmail.com (AG)

OPEN ACCESS

Citation: Ezran C, Bonds MH, Miller AC, Cordier LF, Haruna J, Mwanawabenea D, et al. (2019) Assessing trends in the content of maternal and child care following a health system strengthening initiative in rural Madagascar: A longitudinal cohort study. PLoS Med 16(8): e1002869. https://doi.org/10.1371/journal.pmed.1002869

Academic Editor: Lars Åke Persson, London School of Hygiene and Tropical Medicine, UNITED KINGDOM

Received: March 15, 2019

Accepted: July 19, 2019

Published: August 20, 2019

Data Availability Statement: All data relevant to this study are available from the Harvard Dataverse data repository (Harvard Dataverse, V1, https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/LSEW2L, UNF:6:1hz3FbZt9I4JdVgSNYyIFA== [fileUNF]).

Funding: The authors received no external source of funding for this work. The IHOPE and SARA studies were funded by the nongovernmental

Abstract

Background

In order to reach the health-related Sustainable Development Goals (SDGs) by 2030, gains attained in access to primary healthcare must be matched by gains in the quality of services delivered. Despite the broad consensus around the need to address quality, studies on the impact of health system strengthening (HSS) have focused predominantly on measures of healthcare access. Here, we examine changes in the content of maternal and child care as a proxy for healthcare quality, to better evaluate the effectiveness of an HSS intervention in a rural district of Madagascar. The intervention aimed at improving system readiness at all levels of care (community health, primary health centers, district hospital) through facility renovations, staffing, equipment, and training, while removing logistical and financial barriers to medical care (e.g., ambulance network and user-fee exemptions).

Methods and findings

We carried out a district-representative open longitudinal cohort study, with surveys administered to 1,522 households in the Ifanadiana district of Madagascar at the start of the HSS intervention in 2014, and again to 1,514 households in 2016. We examined changes in healthcare seeking behavior and outputs for sick-child care among children <5 years old, as well as for antenatal care and perinatal care among women aged 15–49. We used a difference-in-differences (DiD) analysis to compare trends between the intervention group (i.e., people living inside the HSS catchment area) and the non-intervention comparison group (i.e., the rest of the district). In addition, we used health facility–based surveys, monitoring service availability and readiness, to assess changes in the operational capacities of

organization PIVOT and the Herrnstein Family Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: some authors are current or former employees of institutions discussed in this article, including the nongovernmental organization PIVOT and the Government of Madagascar. MHB is cofounder and scientific director of PIVOT; ACM is senior research advisor of PIVOT; LFC is monitoring and evaluation coordinator of PIVOT; JH is medical programs coordinator of PIVOT; DM is former medical point of contact of PIVOT; MR and H-TRR are, respectively, head of and data analyst for the Demography and Social Statistics unit at the National Institute of Statistics of Madagascar; MAO is former country director of PIVOT, BRR is monitoring and evaluation manager of PIVOT; MM is a member of the Editorial Board of *PLOS Medicine*; and AG is research adviser of PIVOT.

Abbreviations: CHW, community health worker site; DHS, Demographics and Health Survey; DiD, difference-in-differences; GPS, global positioning system; HSS, health system strengthening; IHOPE, The Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation; IMCI, Integrated Management of Childhood Illness; INSTAT, National Institute of Statistics; MoH, Ministry of Health; NSAID, nonsteroidal anti-inflammatory drug; PAUSENS, Emergency Support to Critical Education, Health and Nutrition Services; PHF, public health facility; SARA, Service Availability and Readiness Assessment; SDG, Sustainable Development Goal; SPA, Service Provision Assessment; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TIDieR, Template for Intervention Description and Replication; UHC, universal health coverage; USAID, United States Agency for International Development; WHO, World Health Organization.

facilities supported by the intervention. The cohort study included 657 and 411 children (mean age = 2 years) reported to be ill in the 2014 and 2016 surveys, respectively (27.8% and 23.8% in the intervention group for each survey), as well as 552 and 524 women (mean age = 28 years) reported to have a live birth within the previous two years in the 2014 and 2016 surveys, respectively (31.5% and 29.6% in the intervention group for each survey). Over the two-year study period, the proportion of people who reported seeking care at health facilities experienced a relative change of +51.2% (from 41.4% in 2014 to 62.5% in 2016) and −7.1% (from 30.0% to 27.9%) in the intervention and non-intervention groups, respectively, for sick-child care (DiD *p*-value = 0.01); +11.4% (from 78.3% to 87.2%), and +10.3% (from 67.3% to 74.2%) for antenatal care (*p*-value = 0.75); and +66.2% (from 23.1% to 38.3%) and +28.9% (from 13.9% to 17.9%) for perinatal care (*p*-value = 0.13). Most indicators of care content, including rates of medication prescription and diagnostic test administration, appeared to increase more in the intervention compared to in the non-intervention group for the three areas of care we assessed. The reported prescription rate for oral rehydration therapy among children with diarrhea changed by +68.5% (from 29.6% to 49.9%) and −23.2% (from 17.8% to 13.7%) in the intervention and non-intervention groups, respectively (*p*-value = 0.05). However, trends observed in the care content varied widely by indicator and did not always match the large apparent increases observed in care seeking behavior, particularly for antenatal care, reflecting important gaps in the provision of essential health services for individuals who sought care. The main limitation of this study is that the intervention catchment was not randomly allocated, and some demographic indicators were better for this group at baseline than for the rest of the district, which could have impacted the trends observed.

Conclusion

Using a district-representative longitudinal cohort to assess the content of care delivered to the population, we found a substantial increase over the two-year study period in the prescription rate for ill children and in all World Health Organization (WHO)-recommended perinatal care outputs assessed in the intervention group, with more modest changes observed in the non-intervention group. Despite improvements associated with the HSS intervention, this study highlights the need for further quality improvement in certain areas of the district's healthcare system. We show how content of care, measured through standard population-based surveys, can be used as a component of HSS impact evaluations, enabling healthcare leaders to track progress as well as identify and address specific gaps in the provision of services that extend beyond care access.

Author summary

Why was this study done?

- One of the largest contributors to preventable deaths in low- and middle-income countries is poor quality of care delivered by the public health system. Yet, given the multiple dimensions of care quality, there are currently no standard measures to evaluate impacts in this domain.

- While health system strengthening (HSS) initiatives strive to simultaneously increase access to healthcare and improve care quality, few studies have evaluated the impact of HSS initiatives on both targets. Our study sought to determine whether an HSS intervention in a rural health district of Madagascar, one of the world's poorest countries, improved the quality of maternal and child care at the population level.

What did the researchers do and find?

- We used data from a district-representative open longitudinal cohort that followed over 1,500 households between 2014 and 2016, in order to compare trends in the content of care as a proxy for care quality, inside and outside the intervention catchment, through difference-in-differences analyses. We also analysed data from a Service Availability and Readiness Assessment (SARA) conducted in health facilities supported by the HSS intervention.
- Our data set included self-reported information on health seeking behaviors and care content for common illnesses of children under five (n = 657 in 2014; 411 in 2016), and for maternal care before and during live births that occurred in the previous two years (n = 552 in 2014; 524 in 2016).
- We found that compared to the non-intervention group, the intervention group experienced a larger improvement in most care content outputs for childhood illnesses (e.g., 24.4% more children with diarrhea were prescribed oral rehydration therapy after two years than in the non-intervention area) and for perinatal care, whereas trends in antenatal care content were more similar in both populations.
- Despite progress, there remained important gaps in the provision of essential health services for individuals in both the intervention and non-intervention groups.

What do these findings mean?

- The study provides evidence that HSS initiatives can successfully increase access to healthcare in target populations while also improving the quality of certain primary care services provided.
- The approach used here can be adapted to other local HSS initiatives to stimulate more comprehensive impact evaluations.
- Evidence from this study can help guide investments in integrated primary care systems that are needed globally to improve maternal and child care.
- The interpretation of the study findings is limited by the absence of randomization in the allocation of the intervention's programs and by the reliance on self-reported answers.

Introduction

The advent of the United Nations Sustainable Development Goals (SDGs) in 2015 bolstered a global commitment towards achieving universal health coverage (UHC) for all populations by

2030 through strengthened primary care [1,2]. As the 40th anniversary of the Declaration of Alma-Ata for UHC was recently celebrated [3], an estimated 60% of the world's population has access to quality essential healthcare services, medicines, and vaccines, as well as financial risk protection [4]. Although achieving UHC for the remaining approximately 3 billion people in the next decade will require substantial investment [5], recent progress in several low- and middle-income countries such as Cambodia and Rwanda suggests that this ambitious goal is within reach [6]. Their gains in health coverage have been attributed in large part to reductions in financial barriers and sustained investments to strengthen the health system across the entire continuum of care [7,8].

In an effort to promote evidence-based models of health system strengthening (HSS) that can be scaled up nationwide and across borders, the global health community has urged for more rigorous evaluation of the impact of such interventions [9,10]. While past studies evaluating HSS initiatives predominantly focused on measures of access to healthcare ("care seeking behavior" or "coverage"), it is now evident that improving access alone is not sufficient to achieve the health-related SDGs [11–13]. There is growing recognition that measuring care quality is necessary to more comprehensively assess an intervention's effectiveness in improving population health outcomes [14–17].

The Lancet Global Health Commission on High Quality Health Systems defines 10 essential components of high-quality health systems, including better health outcomes, competent care, positive user experience, and governance (**S1 Appendix**) [10]. Given the number of contributors to effective healthcare, there are dozens of possible measurable outcomes to evaluate care quality impacts of HSS interventions, ranging from measures of population health outcomes (e.g., disease incidence rates, mortality rates) to more targeted indicators (e.g., care provider performance assessments, vaccination rates) [18–21]. However, such indicators of care quality currently lack standardization, limiting the ability to compare across studies and produce generalizable conclusions [10,22].

The term "content of care" refers to the activity outputs of an intervention, including the medications prescribed, diagnostic tests performed, and counseling provided to patients [18]. Determining the rate of healthcare outputs, such as the provision of recommended diagnoses and treatments, helps assess an aspect of care quality (competent care) in a manner that is quantifiable, objective, and applicable to a variety of diseases and conditions. While there have been increasing efforts in recent years to understand content of care in low resource settings [23–26], the integration of this measure in impact evaluations of HSS interventions using population-level data remains scarce [7].

We evaluate the impact of an HSS intervention on the content of care delivered to a target population in rural Madagascar. Madagascar is one of the poorest countries, with among the lowest per capita healthcare spending in the world [27]. Consequently, the public health system lacks resources to ensure appropriate service provision to its population of 27 million. As of 2012, there were approximately 3.6 physicians, nurses, and midwives per 10,000 people [28], one tenth of the minimal threshold density (34.5 per 10,000) considered necessary to achieve high coverage for essential health services [29]. That same year, the national maternal, under-five, and neonatal mortality rates were 478/100,000 live births, 62/1,000, and 26/1,000, respectively [30]. In 2014, the nongovernmental organization PIVOT partnered with Madagascar's Ministry of Health (MoH) to create a model health system within the government district of Ifanadiana through strengthening the existing public healthcare system with improving facility readiness, clinical programs, and integrated data systems at all levels of care [31,32].

We build on a previously published evaluation that revealed rapid increases in care seeking behavior to health centers and decreases in neonatal and under-five mortality rates associated with the HSS intervention [33]. Using the same district-representative longitudinal cohort

study [34], we examine changes in the content of care provided to the population over the same period. We focus on three areas of healthcare that have a demonstrated impact on maternal and child mortality rates: sick-child care (<5 years old), antenatal care, and perinatal care [35,36]. In addition, we assess changes in the level of service availability (the physical presence of services) and readiness (the components required to provide services)—measures necessary for the provision of quality care [37]—in primary health centers supported by the PIVOT-MoH initiative. By evaluating changes in content of care at the population level, we thus deepen our understanding of the impact of an HSS intervention in a way that weighs accessibility and quality as complementary components of effective healthcare delivery.

Methods

Study intervention

Since 2014, PIVOT and Madagascar's MoH have collaborated to design, implement, and assess an HSS intervention in the southeastern district of Ifanadiana (**Fig 1**) as a model healthcare delivery system for the country [31,32]. In the first two years of the intervention, the PIVOT--MoH partnership primarily focused on a catchment area that included 4 out of the district's 13 communes, encompassing approximately one third of the 200,000 people living in Ifanadiana. This initial intervention area contains the district's sole hospital and four of its primary health centers. The choice of the catchment area was done according to logistical and programmatic reasons, and there was no randomization of communes involved. Guided by the World Health Organization's (WHO) framework for functional HSS [9], the partnership targeted all three levels of care governed by the MoH in the catchment area (community health, primary health centers, district hospital) [32]. In brief, to improve readiness, PIVOT-MoH renovated, staffed, and equipped the hospital and health centers located in the catchment area since mid-2014, as well as initiated a community health program in a subset of the catchment's remote villages by November 2015. In addition, the partnership sought to remove logistical and financial barriers to medical care by creating an ambulance network and removing fees for commonly prescribed medications for all patients [38]. PIVOT-MoH also implemented WHO's Integrated Management of Childhood Illness (IMCI) guidelines [39] and national guidelines for the treatment for severe acute malnutrition, as well as had social workers at health facilities for the accompaniment and follow-up of vulnerable patients. Details on the intervention are available in S1 TIDIER checklist using the Template for Intervention Description and Replication (TIDieR) [40].

During this period, two independent groups implemented complementary health programs in the Ifanadiana district. The World Bank–funded Emergency Support to Critical Education, Health and Nutrition Services (PAUSENS) project created a basic package of health, nutrition, and reproductive health services in the district's 13 primary health centers (Centre de Santé de Base 2), available free of charge to all pregnant women and children under 5 years [41]. This program provided equipment and medication for pharmacies and health centers, as well as training for obstetrics and neonatal care. Second, the United States Agency for International Development (USAID) funded Mikolo project provided some training and limited supervision for 150 community health workers stationed in remote villages (approximately half located inside the PIVOT-MoH catchment area) on monitoring and counseling for basic health practices in their community [42]. The main difference in healthcare provision between the PIVOT-MoH catchment area and the rest of the Ifanadiana district was the support in infrastructure building, training and staffing, removal of user fees, and additional support to guideline implementation of clinical programs provided by PIVOT.

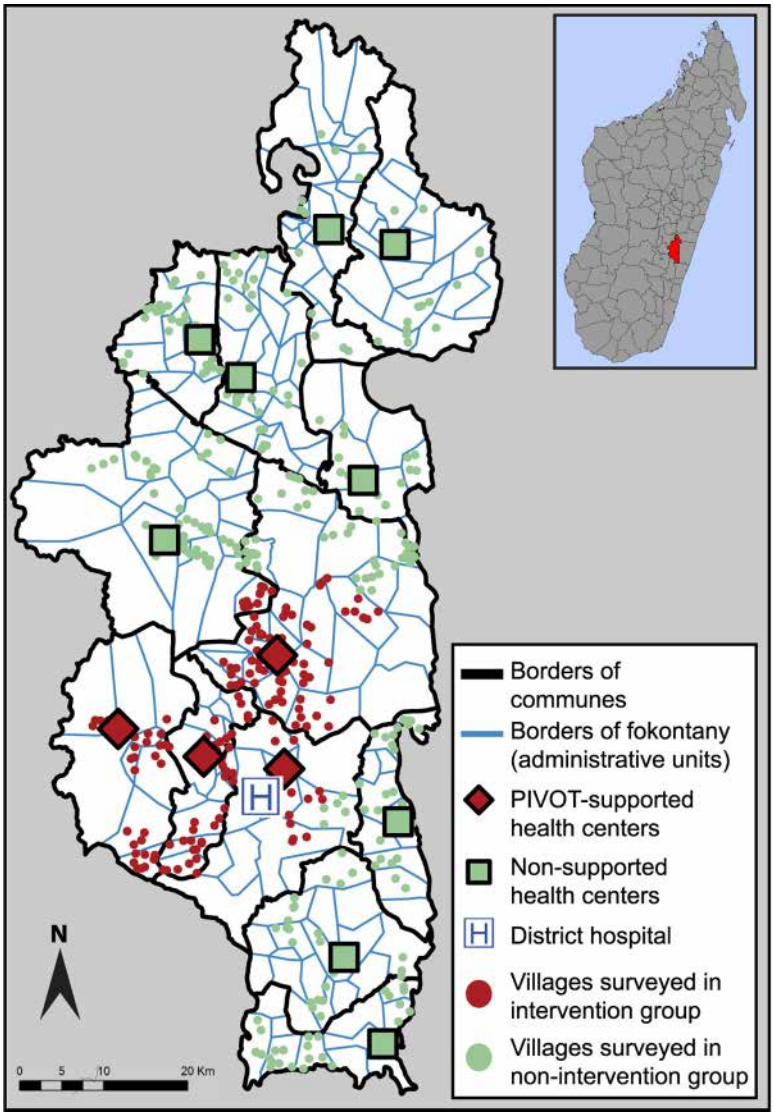

Fig 1. Map of the Ifanadiana district in southeastern Madagascar. Ifanadiana has an estimated population of 200,000 people, approximately one third of which live within PIVOT's initial catchment area. The district is comprised of 13 communes (demarcated by black lines) and 195 fokontany (the smallest administrative unit, demarcated by blue lines). Each of the communes contains a primary health center (Centre de Santé de Base 2: red diamonds and green squares). Between 2014 and 2016, PIVOT and the MoH renovated, staffed, and equipped four of them (red diamonds). The households surveyed by the PIVOT-MoH longitudinal cohort study that were located in villages nearest to a PIVOT-supported health center were categorized into the intervention group (red dots); the households located in villages nearest to a nonsupported health center were categorized into the non-intervention group (green dots). Map of Madagascar in the top right corner, with the Ifanadiana district colored in red. Base maps obtained from INSTAT and GADM.org. INSTAT, National Institute of Statistics; MoH, Ministry of Health.

https://doi.org/10.1371/journal.pmed.1002869.g001

Data collection

Household surveys (IHOPE cohort). We collaborated with Madagascar's National Institute of Statistics (INSTAT) to create an ongoing open longitudinal cohort study of 1,600 households (the sample size required to estimate under-five mortality within a 12% margin of error) representative of the Ifanadiana district's population—The Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation (IHOPE) [34]. The households were selected through a

two-stage cluster sampling scheme. Maps from the 2009 census were used to divide the district into 169 geographical clusters, after which 40 clusters from within and 40 clusters from outside the initial catchment area were chosen at random, with probabilities proportional to population size (Fig 1). Within each cluster, an enumeration was done to obtain a complete household listing, and 20 households were randomly selected prior to conducting the survey. A questionnaire adapted from the Demographics and Health Survey (DHS) [43] was administered in person to all men aged 15–59 and women aged 15–49 living in the enrolled households at baseline (April–May 2014). This survey was repeated two years after the initiation of the intervention (August–September 2016). Households that were unavailable or declined participation in the second survey were replaced with additional households from the original sampling lists; families and individuals that moved into original households were also included in the second survey (for details, see Miller and colleagues [34]). We collected data on household characteristics, socioeconomic status, and maternal and child health, among others. Overall, among the 1,600 households sampled in each survey, 1,522 provided data in 2014 and 1,514 in 2016 (95.1% and 94.6% response rate, respectively).

Health facility assessments (SARA survey). To measure changes in service availability throughout PIVOT's HSS intervention, we conducted facility surveys in 2014 and 2015 at the four PIVOT-support health centers in the catchment area. These were based on the WHO Service Availability and Readiness Assessment (SARA) framework [44], which was adapted to the Malagasy health system context and norms. We assessed availability of preventative and therapeutic services, health facility personnel level, supply of essential medicines, and basic functional medical equipment, among others (S1 Appendix). Evaluations of non-PIVOT supported health centers were not conducted at that time. Hospital-level norms for service availability and readiness were updated by the MoH during the study period, precluding a longitudinal follow-up and analysis of the district hospital from baseline values.

The IHOPE survey was approved by the Madagascar National Ethics Committee and Harvard Medical School's IRB. Verbal consent was obtained from adults (18–59 years old) and from parents or legal guardians for their children (under 18 years), with assent from minors (15–18 years old) to participate in the study. The SARA survey was authorized by the MoH. We carried out our analysis on de-identified data. We reported this study as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [45], which are available in S1 STROBE checklist.

Outcomes

A prospective analysis plan for measuring changes in care seeking behavior was designed as part of the IHOPE cohort study and has been published in Miller and colleagues (2018) [34]. The current analysis of content of care was done retrospectively in 2017 to provide complementary insights around healthcare quality. We focused on three areas of healthcare: sick-child care, antenatal care, and perinatal care. To benchmark appropriate care, we used as our standard WHO's IMCI guidelines [39], as well as their guidelines for maternal and newborn health [46,47] (S1 Appendix). Based on the parents' responses, sick-child care seeking was measured as the proportion of children under five who had diarrhea (symptom of possible gastroenteritis), persistent cough with difficulty breathing (symptoms of possible acute respiratory infection), or fever (symptom of possible malaria infection) within the previous two weeks and who were brought to care for that indication either at one of MoH's public health facilities (PHFs)—which includes the district hospital and the district's primary health centers—or at any of the community health worker sites (CHWs) located throughout the district. The content of sick-child care was assessed by examining a variety of treatments and diagnostic

procedures that ill children could receive for a particular symptom in accordance with IMCI guidelines. For each possible treatment, we measured the proportion of symptomatic children to whom it was prescribed at a PHF or CHW, as reported by parents in the IHOPE surveys.

We examined antenatal and perinatal care among women aged 15–49 who had a live birth within the previous two years. Antenatal care seeking was assessed using three indicators: the proportion of pregnant women who attended an antenatal consultation at a PHF (a) at least once in their pregnancy, (b) at least four times, and (c) at least once during their first trimester. Perinatal care seeking was measured as the proportion of women who delivered at a PHF. Content of antenatal care was assessed by examining the coverage of several screening tests pregnant women reported to have received during at least one of their antenatal consultations at a PHF. For perinatal care, we assessed the rate of recommended newborn and maternal health assessments that women reported in the IHOPE surveys following their child's delivery at a PHF.

Based on results from the SARA surveys conducted in PIVOT-supported health centers, we examined the availability of the following services: (a) preventative services, (b) therapeutic services, (c) health promotion and administration services, and (d) complementary services (e.g., tuberculosis care, malnutrition care). We also examined health centers' readiness to provide general healthcare services based on levels of (a) personnel (b) basic amenities (e.g., power source, water source), (c) basic equipment, and (d) essential medicines. For each indicator of service availability and readiness, we measured the available proportion of components included in the indicator, as defined by MoH/WHO standards (**S1 Appendix**).

Data analysis

Given that the vast majority of the district's population accesses health centers by foot, we stratified participants of the IHOPE surveys into an intervention and a non-intervention group based on geographic proximity of their household to a PIVOT-supported or nonsupported health center (**Fig 1**). Using the global positioning system (GPS) coordinates of each health center and each of the 80 geographical clusters randomly sampled (centroid of all the villages in a cluster), we identified the health center that was the shortest Euclidean distance away from a given cluster. We considered participants to be in the intervention group if they lived in households located in a cluster for which the nearest facility was a PIVOT-supported health center and in the non-intervention group otherwise.

Using the standard protocols for DHS surveys [48], all results from the IHOPE surveys were adjusted using sampling weights, which account for the unequal probability of household selection, depending on the population size of each cluster surveyed and nonresponse rates. We did not adjust for potential spatial autocorrelation through mixed effects models. We used a chi-squared statistic to assess differences between outcomes in the intervention and non-intervention group for each year, and a difference-in-differences (DiD) regression analysis to estimate the overall effect of PIVOT-MoH's intervention over time (**S1 Appendix**). We also compared DiD estimates, unadjusted and adjusted, with household wealth. All results from the SARA surveys were averaged across the four health centers evaluated, and changes over time were reported. We analyzed all data with R software using the "survey," "ggplot2," "sp," "maptools," "rgeos," and "foreign" packages.

Results

The IHOPE study included 1,333 children under five in the 2014 survey and 1,345 children in the 2016 survey (31.0% and 29.7% in the intervention group, respectively). It also included 1,635 women aged 15–49 in the 2014 survey and 1,585 women in the 2016 survey (39.2% and

37.5% in the intervention group, respectively). While many demographic characteristics were similar between the two groups (Table 1), the household wealth index,maternal education level and literacy rate were higher in the intervention group than in the non-intervention group. The nonresponse rate was low (<2%) for all questions of care seeking behavior and care content assessed, with no significant differences between the two groups observed (S2 Table).

Sick-child care

Over the two-year study period, the proportion of children with reported diarrhea, fever, and/or persistent coughing who sought care rose in the intervention group by 51.2% (from 41.4% in 2014 to 62.5% in 2016), compared with a 7.1% decrease (from 30.0% to 27.9%) in the non-intervention group (DiD p-value = 0.01) (Table 2). This apparent increase in care seeking behavior was predominantly attributable to increased visits to PHFs rather than to CHWs. The proportion of ill children who were prescribed at least one form of medication at a PHF or CHW appeared to increase in the intervention group by 45.2% (from 40.1% to 58.3%) and decrease in the non-intervention group by 8.9% (from 29.6% to 26.9%, DiD p-value = 0.02). However, trends in content of care varied widely by indicator and did not always match trends observed in care seeking behavior (Table 2 and Fig 2). Among the children in the intervention group who were reported with diarrhea in 2016, 61.5% attended a PHF or CHW (+42.0% from 2014 rate) and 49.9% received oral rehydration therapy there (+68.5%), while only 18.6% received zinc supplement (+17.6%)—both of which are recommended for all children with diarrhea by the IMCI guidelines. The prescription rate for antidiarrheal medication, not recommended by IMCI guidelines, dropped from 8.3% to 0% in 2016. Among the children in the intervention group who were reported with fever in 2016, 60.5% attended a PHF or CHW (+-20.4%); however, only 30.8% reported having received a malarial rapid diagnostic test (−21.6%)—a test recommended by IMCI guidelines for all children with fever in malarial endemic areas. In addition, 14.2% received antimalarial medication (−38.5%), and 35.6% received antibiotics (+51.7%), although appropriateness of these prescriptions could not be evaluated based on information reported in the IHOPE surveys. Controlling for household wealth produced similar DiD estimates and associated p-values for all indicators of sick-child care (S1 Table).

Antenatal and perinatal care

Between 2014 and 2016, antenatal care seeking behavior appeared to increase moderately for pregnant women in the intervention group (Table 3 and Fig 3). In the 2016 IHOPE survey, 87.2% of these women attended an antenatal consultation at a PHF at least once during their pregnancy (+11.4% increase from 2014 survey rate); however, only 48.5% attended four or more consultations throughout their pregnancy, and 17.0% attended a consultation within the first trimester of their pregnancy. Results are detailed in S1 Appendix. With regards to content of antenatal care, there were variable increases over the study period in the rates of standard screening tests and measurements, and many indicators remained low in 2016 despite the apparent increase in care seeking behavior (Table 3 and Fig 3). While 77.8% of pregnant women in the intervention group reported in the 2016 survey to have attended at least one consultation at a PHF and had their weight measured (+2.8%), 67.1% had their blood pressure measured (+22.8%), 48.7% had a blood test (+1.1%), and 27.1% had a urine test (+219.4%) during at least one of their consultations—all measurements, except urine tests, recommended by both international and national antenatal care guidelines. Moreover, only 39.1% of pregnant women reported receiving counseling on how to address possible pregnancy

Table 1. Demographic characteristics of women (15–49 years old) and children (<5 years old) participants in the IHOPE cohort. Comparisons of demographic characteristics between the intervention and non-intervention groups were made separately for 2014 and 2016 surveys. Differences between groups for each survey year were calculated using a Student *t* test for continuous variables and a chi-squared test for categorical variables.

Characteristics	2014			2016		
	Non-intervention group *N* (%)	Intervention group *N* (%)	*p*-value	Non-intervention group *N* (%)	Intervention group *N* (%)	*p*-value
Children (<5 years old)	**920**	**413**		**945**	**400**	
Reported sick within two weeks of survey date *By symptom*:	474 (51.5)	183 (44.3)	0.05	313 (33.1)	98 (24.5)	0.00
Diarrhea	125 (13.6)	56 (13.6)	0.96	107 (11.3)	44 (11.0)	0.87
Fever	352 (38.3)	91 (22.0)	0.00	137 (14.5)	27 (6.8)	0.00
Cough and difficulty breathing	251 (27.3)	110 (26.6)	0.87	156 (16.5)	44 (11.0)	0.02
Sex			0.67			0.93
Male	465 (50.5)	203 (49.2)		484 (51.2)	204 (51.0)	
Female	455 (49.5)	210 (50.8)		461 (48.8)	196 (49.0)	
Mean age in years	2.5	2.6	0.39	2.8	2.6	0.27
Mean number of siblings alive	2.7	2.4	0.15	2.7	2.5	0.44
Household wealth index*			0.01			0.00
Within poorest 1st or 2nd wealth quintiles	516 (56.1)	144 (34.9)		525 (55.5)	141 (35.2)	
Within richest 4th or 5th wealth quintiles	236 (25.6)	191 (46.2)		212 (22.5)	189 (47.1)	
Mean maternal age in years	29.0	28.2	0.15	28.5	29.2	0.32
Highest maternal education level attained**			0.00			0.00
Received no formal education	360 (39.1)	89 (21.5)		360 (38.1)	99 (24.8)	
Attained primary education level	506 (55.0)	238 (57.6)		533 (56.4)	213 (53.3)	
Attained secondary education level or higher	54 (5.9)	86 (20.8)		52 (5.5)	88 (22.0)	
Maternal literacy status			0.00			0.00
Not literate	620 (67.4)	159 (38.5)		588 (62.2)	176 (44.0)	
Literate	299 (32.5)	254 (61.5)		356 (37.7)	221 (55.3)	
Women (15–49 years old)	**994**	**641**		**990**	**595**	
Reported delivery within two years of survey date	378 (38.0)	174 (27.1)	0.00	369 (37.3)	155 (26.1)	0.00
Mean age in years	28.4	28.4	0.98	28.7	29.3	0.20
Marital status			0.02			0.00
Not married	372 (37.4)	303 (47.3)		373 (37.7)	273 (45.9)	
Married or lives with a partner	622 (62.6)	338 (52.7)		617 (62.3)	321 (53.9)	
Mean number of live births	3.5	2.9	0.04	3.5	2.9	0.02
Household wealth index*			0.00			0.00
Within poorest 1st or 2nd wealth quintiles	509 (51.2)	154 (23.9)		479 (48.4)	167 (28.2)	
Within richest 4th or 5th wealth quintiles	279 (28.1)	389 (60.7)		293 (29.5)	348 (58.6)	
Highest education level attained**			0.00			0.00
Received no formal education	312 (31.4)	97 (15.1)		294 (29.7)	92 (15.5)	
Attained primary education level	597 (60.1)	318 (49.6)		588 (59.4)	301 (50.6)	
Attained secondary education level or higher	85 (8.6)	226 (35.3)		108 (10.9)	201 (33.8)	
Literacy status			0.00			0.00
Not literate	567 (57.0)	182 (28.4)		548 (55.4)	195 (32.8)	
Literate	423 (42.6)	459 (71.6)		440 (44.4)	398 (66.9)	

*A wealth index was calculated for each household in the Ifanadiana district based on standard DHS methods [48]. Households were categorized into quintiles (20% of Ifanadiana households in each quintile) based on their wealth index score. Households in the first and second wealth quintiles represent the poorest 40% of the population, while households in the fourth and fifth quintiles represent the richest 40% of the population.

**The education level attained was based on the highest grade level women reported to be attending or have completed at time of the survey.

Abbreviations: DHS, Demographics and Health Survey; IHOPE, The Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation.

https://doi.org/10.1371/journal.pmed.1002869.t001

Table 2. Summary of responses and trends from the 2014 and 2016 IHOPE surveys on indicators of sick-child care seeking behavior and care content (children <5 years old).

Indicator		2014			2016			2014–2016 Trend		
	Study group	*N*	Percent (SE)	Difference (*p*-value)	*N*	Percent (SE)	Difference (*p*-value)	Percent relative change	Percent absolute change	DiD (*p*-value)
Summary statistics for all children with symptoms of diarrhea, fever, and/or coughing with difficulty breathing										
Visit to a PHF or CHW	IG	183	41.35 (5.33)	—	98	62.50 (7.42)	—	51.17	21.16	—
	NG	474	30.02 (3.35)	11.32 (0.07)$^{+}$	313	27.88 (3.97)	34.62 (0.00)***	−7.13	−2.14	23.29 (0.01)**
Visit to a PHF	IG	183	28.98 (5.43)	—	98	49.66 (7.04)	—	71.37	20.68	—
	NG	474	22.23 (3.34)	6.75 (0.28)	313	22.10 (3.50)	27.56 (0.00)***	−0.56	−0.12	20.81 (0.00)***
Visit to a CHW	IG	183	12.85 (3.91)	—	98	12.84 (5.06)	—	−0.09	−0.01	—
	NG	474	7.98 (1.95)	4.87 (0.23)	313	5.78 (2.52)	7.06 (0.17)	−27.61	−2.20	2.19 (0.74)
Any treatment prescribed at a PHF or CHW	IG	183	40.14 (5.53)	—	98	58.26 (7.73)	—	45.16	18.12	—
	NG	474	29.56 (3.31)	10.58 (0.10)$^{+}$	313	26.93 (3.95)	31.33 (0.00)***	−8.89	−2.63	20.75 (0.02)*
Care seeking for children with diarrhea										
Visit to a PHF or CHW	IG	56	43.28 (9.88)	—	44	61.47 (8.41)	—	42.03	18.19	—
	NG	125	31.02 (5.90)	12.26 (0.28)	107	31.45 (5.30)	30.02 (0.00)***	1.37	0.43	17.76 (0.16)
Visit to a PHF	IG	56	35.96 (10.01)	—	44	45.29 (10.78)	—	25.95	9.33	—
	NG	125	21.95 (5.27)	14.01 (0.19)	107	26.97 (5.30)	18.32 (0.12)	22.87	5.02	4.31 (0.74)
Visit to a CHW	IG	56	7.32 (4.97)	—	44	16.18 (9.15)	—	120.98	8.86	—
	NG	125	9.07 (3.37)	-1.75 (0.78)	107	4.48 (1.86)	11.70 (0.06)$^{+}$	−50.63	−4.59	13.45 (0.21)
Content of care for children with diarrhea										
Any treatment prescribed at a PHF or CHW	IG	56	41.50 (10.04)	—	44	58.30 (8.80)	—	40.48	16.80	—
	NG	125	27.69 (6.23)	13.80 (0.23)	107	22.42 (4.75)	35.88 (0.00)***	−19.05	−5.28	22.07 (0.13)
Oral rehydration therapy prescribed at a PHF or CHW	IG	56	29.64 (6.81)	—	44	49.93 (10.52)	—	68.48	20.30	—
	NG	125	17.78 (5.47)	11.86 (0.18)	107	13.65 (3.37)	36.28 (0.00)***	−23.22	−4.13	24.43 (0.05)*
Antibiotics prescribed at a PHF or CHW	IG	56	24.19 (7.08)	—	44	15.88 (7.09)	—	−34.34	−8.31	—
	NG	125	14.71 (3.89)	9.48 (0.21)	107	10.71 (3.08)	5.17 (0.46)	−27.18	−4.00	−4.31 (0.67)
Zinc supplements prescribed at a PHF or CHW	IG	56	15.81 (4.66)	—	44	18.59 (11.47)	—	17.61	2.78	—
	NG	125	6.78 (2.80)	9.03 (0.09)$^{+}$	107	3.19 (1.79)	15.40 (0.03)*	−52.97	−3.59	6.38 (0.65)
Antidiarrheal medication prescribed at a PHF or CHW	IG	56	8.32 (6.66)	—	44	0.00 (0.00)	—	−100.00	−8.32	—
	NG	125	1.52 (1.08)	6.80 (0.08)$^{+}$	107	0.00 (0.00)	—	−100.00	−1.52	−6.80 (0.32)
Homemade remedy prescribed at a PHF or CHW	IG	56	0.00 (0.00)	—	44	0.00 (0.00)	—	0.00	0.00	—
	NG	125	2.97 (2.09)	−2.97 (0.34)	107	0.53 (0.53)	−0.53 (0.54)	−82.33	−2.45	2.45 (0.26)
Care seeking for children with persistent cough and difficulty breathing										
Visit to a PHF or CHW	IG	110	38.46 (5.32)	—	44	58.97 (11.24)	—	53.31	20.50	—
	NG	251	27.85 (4.05)	10.61 (0.11)	156	28.29 (4.54)	30.67 (0.01)**	1.58	0.44	20.06 (0.08)$^{+}$
Visit to a PHF	IG	110	28.83 (5.63)	—	44	49.28 (10.48)	—	70.97	20.46	—
	NG	251	22.77 (3.67)	6.06 (0.36)	156	21.90 (3.96)	27.38 (0.01)**	−3.80	−0.87	21.32 (0.03)*
Visit to a CHW	IG	110	9.64 (3.15)	—	44	9.68 (5.21)	—	0.48	0.05	—
	NG	251	5.08 (1.86)	4.55 (0.19)	156	6.39 (3.13)	3.29 (0.57)	25.71	1.31	−1.26 (0.84)
Content of care for children with persistent cough and difficulty breathing										
Any treatment prescribed at a PHF or CHW	IG	110	37.35 (5.81)	—	44	47.85 (10.38)	—	28.10	10.50	—
	NG	251	27.54 (4.05)	9.81 (0.16)	156	28.29 (4.54)	19.56 (0.07)$^{+}$	2.73	0.75	9.74 (0.40)

(*Continued*)

Table 2. (Continued)

Indicator		2014			2016			2014–2016 Trend		
	Study group	*N*	Percent (SE)	Difference (*p*-value)	*N*	Percent (SE)	Difference (*p*-value)	Percent relative change	Percent absolute change	DiD (*p*-value)
Antibiotics prescribed at a PHF or CHW	IG	110	26.32 (4.83)	—	44	45.12 (10.43)	—	71.43	18.80	—
	NG	251	16.95 (3.65)	9.37 (0.12)	156	17.47 (3.48)	27.65 (0.00)***	3.08	0.52	18.28 (0.13)
NSAIDs/paracetamol prescribed at a PHF or CHW	IG	110	29.59 (4.69)	—	44	23.40 (6.85)	—	−20.92	−6.19	—
	NG	251	21.03 (3.81)	8.56 (0.16)	156	20.30 (4.02)	3.10 (0.69)	−3.48	−0.73	−5.46 (0.48)
Antimalarial medication prescribed at a PHF or CHW	IG	110	8.61 (2.89)	—	44	0.00 (0.00)	—	−100.00	−8.61	—
	NG	251	11.56 (2.43)	−2.95 (0.45)	156	5.90 (2.53)	−5.90 (0.18)	−48.98	−5.66	−2.95 (0.46)
Care seeking for children with fever										
Visit to a PHF or CHW	IG	91	50.26 (6.38)	—	27	60.52 (12.36)	—	20.41	10.26	—
	NG	352	31.25 (3.87)	19.00 (0.01)**	137	33.48 (6.00)	27.03 (0.05)*	7.13	2.23	8.03 (0.57)
Visit to a PHF	IG	91	28.83 (7.31)	—	27	51.15 (12.25)	—	77.44	22.32	—
	NG	352	24.37 (4.16)	4.46 (0.59)	137	29.29 (5.74)	21.86 (0.10)+	20.18	4.92	17.41 (0.25)
Visit to a CHW	IG	91	21.43 (5.97)	—	27	9.36 (5.83)	—	−56.30	−12.07	—
	NG	352	6.88 (1.77)	14.55 (0.00)***	137	4.20 (2.17)	5.17 (0.32)	−39.04	−2.69	−9.38 (0.30)
Content of care for children with fever										
Any treatment prescribed at a PHF or CHW	IG	91	50.26 (6.38)	—	27	52.76 (12.59)	—	4.99	2.51	—
	NG	352	30.63 (3.79)	19.63 (0.01)**	137	31.37 (5.79)	21.39 (0.12)	2.43	0.74	1.76 (0.90)
NSAIDs/paracetamol prescribed at a PHF or CHW	IG	91	39.63 (4.91)	—	27	39.16 (10.50)	—	−1.18	−0.47	—
	NG	352	25.20 (3.83)	14.43 (0.02)*	137	25.60 (5.27)	13.57 (0.23)	1.57	0.40	−0.87 (0.95)
Antibiotics prescribed at a PHF or CHW	IG	91	23.49 (4.45)	—	27	35.63 (11.75)	—	51.67	12.14	—
	NG	352	19.13 (3.10)	4.36 (0.42)	137	17.78 (5.12)	17.85 (0.13)	−7.08	−1.35	13.49 (0.31)
Malarial rapid diagnostic test administered at a PHF or CHW	IG	91	39.26 (7.50)	—	27	30.78 (9.97)	—	−21.60	−8.48	—
	NG	352	20.98 (4.00)	18.28 (0.03)*	137	20.28 (4.66)	10.50 (0.31)	−3.30	−0.69	−7.79 (0.53)
Antimalarial medication prescribed at a PHF or CHW	IG	91	22.99 (5.20)	—	27	14.15 (7.10)	—	−38.45	−8.84	—
	NG	352	15.10 (2.60)	7.89 (0.15)	137	12.24 (4.15)	1.91 (0.81)	−18.92	−2.86	−5.98 (0.50)

+*p*-value < 0.10.

**p*-value < 0.05.

***p*-value < 0.01.

****p*-value < 0.001.

Abbreviations: CHW, community health worker site; DiD, difference-in-differences; IG, intervention group; IHOPE, The Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation; NG, non-intervention group; NSAID, nonsteroidal anti-inflammatory drug; PHF, public health facility.

https://doi.org/10.1371/journal.pmed.1002869.t002

complications (+33.4%). No significant differences in trends for care seeking behavior or content of antenatal care were observed between the intervention and non-intervention groups, although the intervention group appeared to have consistently higher rates for all indicators.

In contrast to antenatal care, perinatal care seeking behavior appeared to increase substantially for pregnant women in the intervention group over the study period, and trends in the content of perinatal care more closely paralleled those observed for care seeking (Table 3 and Fig 3). The percentage of pregnant women in the intervention group who delivered a child at a

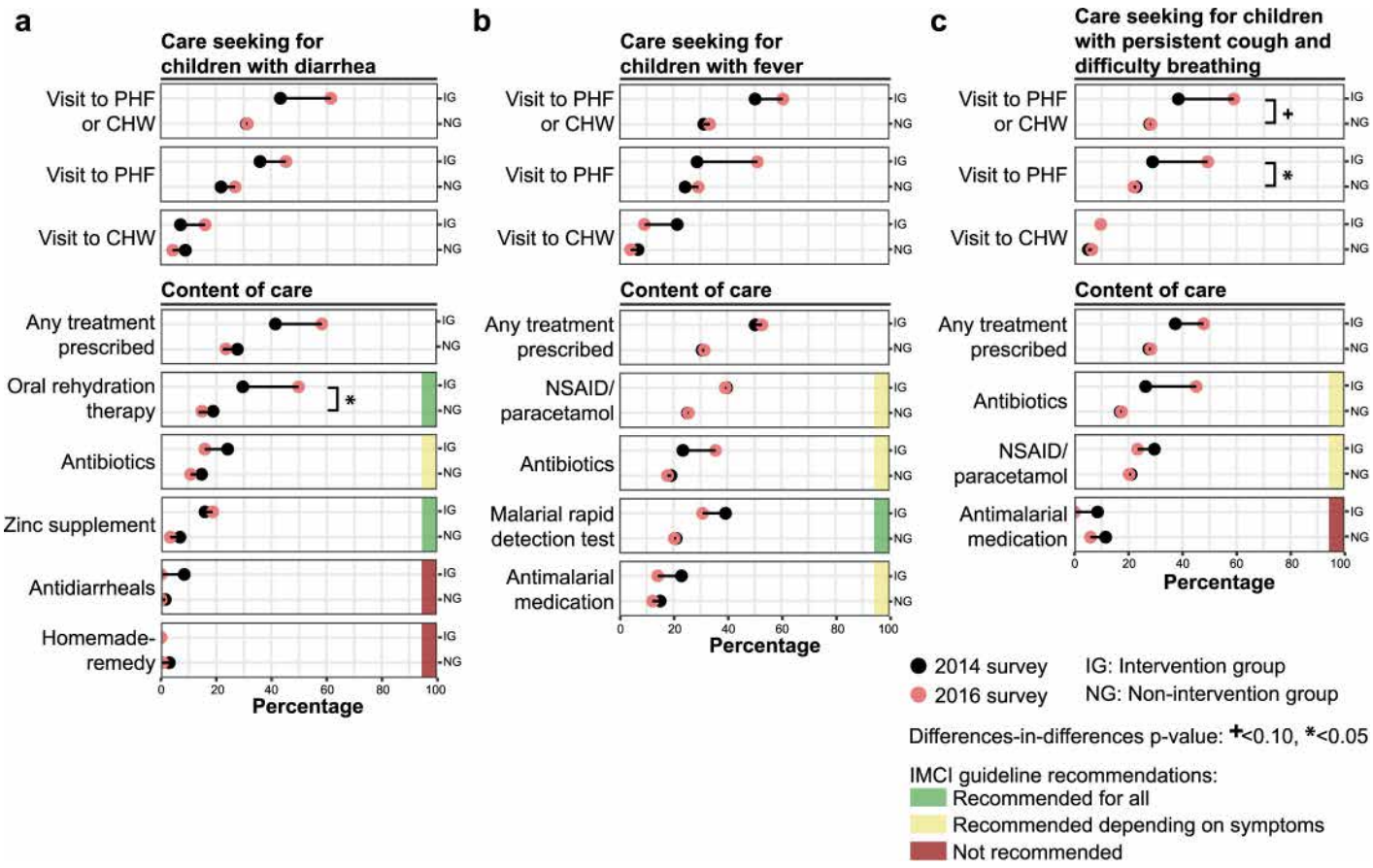

Fig 2. Changes in sick-child care seeking behavior and care content for children (<5 years old) over the first two years of PIVOT-MoH's HSS intervention. Trends were calculated separately for each symptom evaluated: **(a)** diarrhea, **(b)** fever, and **(c)** persistent cough with difficulty breathing. For all outcome indicators, trends over the study period are assessed by tracing from the 2014 percentage value (black dot) to the 2016 percentage value (red dot). Recommendations for treatment are based on WHO's IMCI guidelines (S1 Appendix) [39]. CHW, community health worker site; HSS, health system strengthening; IG, intervention group; IMCI, Integrated Management of Childhood Illness; MoH, Ministry of Health; NG, non-intervention group; NSAID, nonsteroidal anti-inflammatory drug; PHF, public health facility.

https://doi.org/10.1371/journal.pmed.1002869.g002

PHF appeared to increase by 66.2% over the study period (23.1% to 38.3%). Similarly, all content of perinatal care indicators examined appeared to increase by 50%–70% over the study period, and most of these indicators had 2016 rates above 30%, similar to the 2016 rate of PHF-based delivery. In comparison, indicators of care seeking behavior and content of perinatal care for the non-intervention group appeared to minimally change over the study period and remained low in 2016 (2016 rates <18% for all indicators, with <30% increases from 2014 rates).

Service availability and readiness in PIVOT-MoH catchment

Over the first year of the HSS intervention, there was an apparent increase in the mean availability of services in PIVOT-support health centers, across all categories measured in the SARA surveys (Table 4): in 2015, the average health center offered 100.0% of the minimum required preventative services (+14.3% increase from 2014 levels), 100.0% of health promotion and administration services (+9.1%), 90.0% of therapeutic services (+20.0%), and 41.7% of complementary services (+25.0%). Moreover, there was an apparent increase in most categories of general service readiness: in 2015, the average health center had 83.3% of the basic

Table 3. Summary of responses and trends from the 2014 and 2016 IHOPE surveys on indicators of antenatal and perinatal care seeking behavior and care content for women (15–49 years old) and newborns.

Indicator		2014			2016			2014–2016 Trend		
	Study group	*N*	Percent (SE)	Difference (*p*-value)	*N*	Percent (SE)	Difference (*p*-value)	Percent relative change	Percent absolute change	DiD (*p*-value)
Antenatal care seeking for pregnant women										
1 or more consultations at a PHF	IG	174	78.25 (5.48)	—	155	87.20 (3.84)	—	11.44	8.95	—
	NG	378	67.27 (4.40)	10.98 (0.14)	369	74.21 (4.74)	12.99 (0.04)*	10.33	6.95	2.01 (0.75)
4 or more consultations at a PHF	IG	174	38.52 (5.68)	—	155	48.45 (5.86)	—	25.78	9.93	—
	NG	378	26.98 (3.50)	11.54 (0.08)+	369	37.45 (5.24)	11.00 (0.17)	38.79	10.47	−0.54 (0.95)
1 or more consultations at a PHF within the first trimester	IG	174	12.16 (2.67)	—	155	16.95 (3.93)	—	39.48	4.80	—
	NG	378	13.89 (2.39)	−1.73 (0.63)	369	19.45 (3.21)	−2.50 (0.63)	40.05	5.56	−0.76 (0.90)
Content of antenatal care for pregnant women										
Weight measured at a PHF	IG	174	75.69 (5.95)	—	155	77.80 (3.81)	—	2.79	2.11	—
	NG	378	56.61 (4.70)	19.08 (0.02)*	369	67.22 (5.55)	10.58 (0.11)	18.74	10.61	−8.50 (0.18)
Blood pressure measured at a PHF	IG	174	54.67 (5.86)	—	155	67.12 (4.21)	—	22.78	12.45	—
	NG	378	41.03 (3.72)	13.64 (0.05)*	369	57.15 (5.57)	9.97 (0.15)	39.28	16.12	−3.67 (0.66)
Blood sample taken at a PHF	IG	174	48.18 (5.83)	—	155	48.69 (5.01)	—	1.06	0.51	—
	NG	378	23.72 (3.85)	24.46 (0.00)***	369	31.00 (4.40)	17.69 (0.01)**	30.71	7.28	−6.77 (0.29)
Counseled about potential pre-gnancy complications at a PHF	IG	174	29.33 (4.90)	—	155	39.13 (5.15)	—	33.41	9.80	—
	NG	378	18.64 (2.76)	10.68 (0.05)*	369	32.25 (4.48)	6.88 (0.32)	72.98	13.61	−3.81 (0.58)
Urine sample taken at a PHF	IG	174	8.49 (2.74)	—	155	27.11 (4.57)	—	219.4	18.63	—
	NG	378	5.79 (1.47)	2.70 (0.35)	369	16.00 (2.31)	11.12 (0.02)*	176.52	10.21	8.41 (0.19)
Perinatal care seeking for pregnant women and newborns										
Delivery at a PHF	IG	174	23.06 (4.40)	—	155	38.31 (7.63)	—	66.15	15.25	—
	NG	378	13.87 (4.18)	9.19 (0.15)	369	17.87 (3.61)	20.44 (0.01)**	28.87	4.00	11.25 (0.13)
Content of perinatal care for pregnant women and newborns										
Newborn's weight measured at a PHF	IG	174	19.62 (4.34)	—	155	33.00 (6.88)	—	68.17	13.38	—
	NG	378	13.53 (4.13)	6.09 (0.32)	369	10.44 (2.68)	22.56 (0.00)***	-22.88	−3.10	16.47 (0.02)*
Newborn exclusively breastfed for first 3 or more days after delivery at a PHF	IG	174	20.52 (4.16)	—	155	32.25 (6.51)	—	57.14	11.73	—
	NG	378	11.82 (3.46)	8.70 (0.12)	369	14.52 (3.03)	17.73 (0.01)**	22.83	2.70	9.03 (0.16)
Mother's health checked at a PHF within 6 hours of delivery	IG	174	19.71 (3.69)	—	155	30.70 (6.21)	—	55.78	10.99	—
	NG	378	11.41 (3.50)	8.30 (0.12)	369	13.67 (3.30)	17.03 (0.01)**	19.76	2.26	8.74 (0.12)
Newborn's health checked at a PHF within 6 hours of delivery	IG	174	16.25 (3.40)	—	155	27.43 (5.93)	—	68.82	11.18	—
	NG	378	10.58 (3.05)	5.66 (0.23)	369	10.80 (2.34)	16.63 (0.00)***	2.03	0.21	10.97 (0.04)*
Newborn breastfed within 1 hour of delivery at a PHF	IG	174	17.56 (3.79)	—	155	26.41 (6.66)	—	50.39	8.85	—
	NG	378	11.16 (4.13)	6.40 (0.28)	369	14.15 (3.20)	12.26 (0.07)+	26.78	2.99	5.86 (0.43)

+p-value < 0.10.

*p-value < 0.05.

**p-value < 0.01.

***p-value < 0.001.

Abbreviations: CHW, community health worker site; DiD, difference-in-differences; IG, intervention group; IHOPE, The Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation; NG, non-intervention group; PHF, public health facility.

https://doi.org/10.1371/journal.pmed.1002869.t003

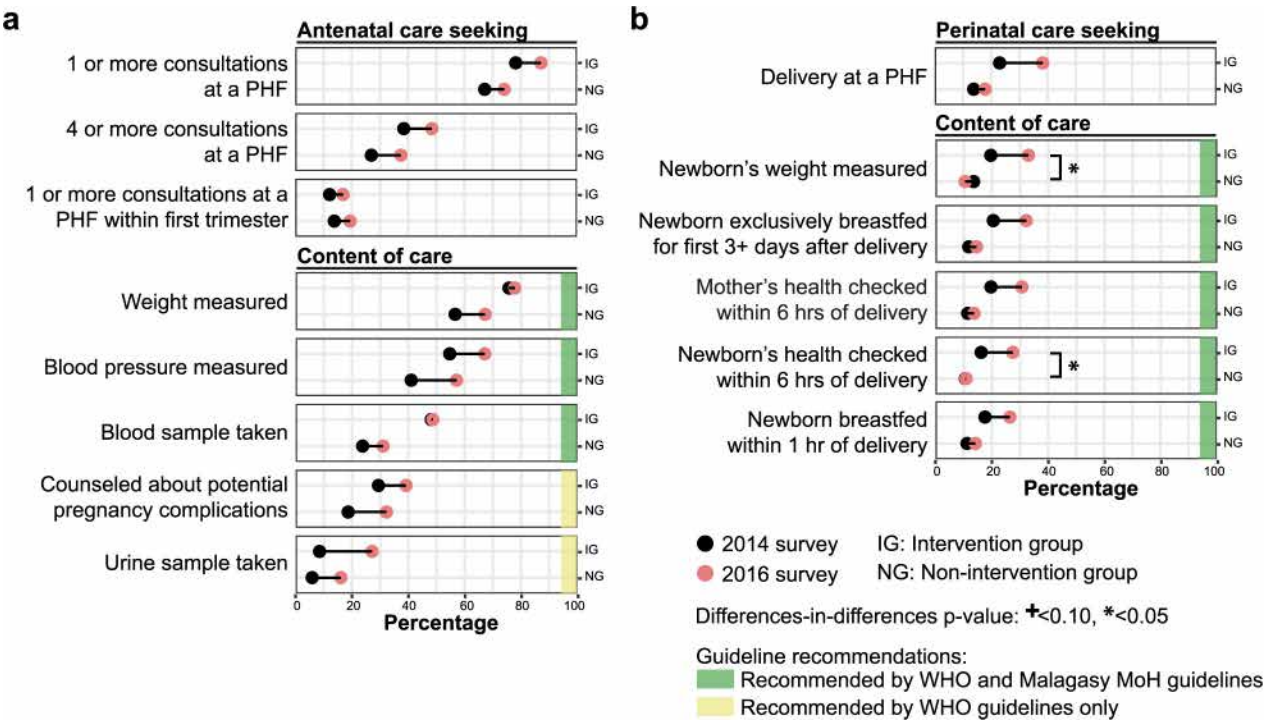

Fig 3. Changes in maternal and newborn care seeking behavior and care content over the first two years of PIVOT-MoH's HSS intervention. Trends were calculated for **(a)** antenatal care and **(b)** perinatal care among women (15–49 years old) who had a delivery within two years of the 2014 and 2016 IHOPE surveys. For all outcome indicators, trends over the study period are assessed by tracing from the 2014 percentage value (black dot) to the 2016 percentage value (red dot). Recommendations for care are based on WHO guidelines (**S1 Appendix**) [46,47]. HSS, health system strengthening; IG, intervention group; IHOPE, The Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation; MoH, Ministry of Health; NG, non-intervention group; PHF, public health facility; WHO, World Health Organization.

https://doi.org/10.1371/journal.pmed.1002869.g003

functional medical equipment components (+66.7%) and 65.0% of the basic health facility amenities (+85.7%). However, only 58.3% of essential medicines were in provision (−23.9%), and the minimum level of health facility personnel required by MoH standards remained at 75.0% both years. Comparisons with service availability and readiness levels in health centers outside the PIVOT-MoH intervention catchment could not be performed because those health centers were not surveyed at the time.

Discussion

Of the 15.6 million avertable deaths that occurred in 2016 in low- and middle-income countries, an estimated 3.6 million were attributable to non-utilization of healthcare services, while 5.0 million were attributable to receipt of low-quality care [49]. In this study, we used an open district-representative longitudinal cohort to assess the content of care delivered to the population in the Ifanadiana district as a proxy for estimating the impact of an integrated HSS initiative on healthcare quality. The results revealed that over the two-year study period, care seeking behavior appeared to have substantially increased in the intervention group compared with the non-intervention group for sick-child care (DiD = 23.3%, p-value = 0.01) and perinatal care (DiD = 11.3%, p-value = 0.13), with a more marginal difference observed between the two groups for antenatal care (DiD = 2.0%, p-value = 0.75).

Despite general improvements in care seeking behavior, there was high variability in the trends observed for indicators of healthcare content in the intervention group. Among children ill with diarrhea, we observed a large increase in the prescription rate of oral rehydration

Table 4. Summary of operational capacities indicators from the 2014 and 2015 SARA surveys. The surveys were conducted at all PIVOT-supported health centers located inside the PIVOT-MoH catchment area. Percentages reported are the available proportion of components in each indicator, averaged across the four health centers assessed.

Indicator	Components of indicator	2014 Percent (SD)	2015 Percent (SD)	Percent relative change	Percent absolute change
Specific service availability					
Preventative services	antenatal care, postnatal care, family planning, childhood immunization	87.50 (14.43)	100.00 (0.00)	14.29	12.50
Therapeutic services	outpatient care, inpatient care, obstetric care, hospitalization capabilities, treatment capabilities	75.00 (19.15)	90.00 (20.00)	20.00	15.00
Health promotion and administration services	health promotion, community outreach, health management information system	91.67 (16.67)	100.00 (0.00)	9.09	8.33
Complementary services	malnutrition care, tuberculosis care, IMCI guidelines implementation	33.33 (0.00)	41.67 (16.67)	25.00	8.33
Overall score		73.33 (5.44)	85.00 (3.33)	15.91	11.67
General service readiness					
Personnel level	1 physician, 1 nurse, 1 midwife, 1 guard, 1 pharmacist	75.00 (25.17)	75.00 (25.17)	0.00	0.00
Basic amenities	power, improved water source, adequate sanitation facilities, communication equipment, sufficient work space	35.00 (25.17)	65.00 (25.17)	85.71	30.00
Basic equipment	adult scale, child scale, thermometer, stethoscope, blood pressure apparatus, examination table	50.00 (0.00)	83.33 (13.61)	66.67	33.33
Essential medicines	aminophylline, amoxicillin, benzylpenicillin, captopril, chlorpheniramine, co-trimoxazole, iron-folic acid, gentamicin, hydrochlorothiazide, ibuprofen, metoclopramide, metronidazole, paracetamol, phenobarbital, oral rehydration therapy/zinc packets	76.67 (8.61)	58.33 (18.98)	−23.91	−18.33
Overall score		64.52 (8.33)	69.00 (3.83)	6.95	4.48

Abbreviations: IMCI, Integrated Management of Childhood Illness; MoH, Ministry of Health; SARA, Service Availability and Readiness Assessment.

https://doi.org/10.1371/journal.pmed.1002869.t004

therapy, matching the apparent increase in care seeking behavior, but a negligible increase for zinc supplementation. We found decreasing rates of malarial rapid diagnostic test administration and antimalarial medication prescriptions over the study period, compared with an increasing percentage of children ill with fever who attended a PHF. These discrepancies may be partially explained as artifacts of when and how the data were collected, including sample size limitations, recall bias, and imperfect knowledge from mothers on the care their children received. Indeed, sample size for children ill with fever was low in the intervention group, given that this group had lower prevalence of fever than the non-intervention group both years. Moreover, the 2016 IHOPE survey was conducted between August and September, which was four months later in the year than the 2014 survey and when the incidence rates of malaria and other infectious diseases are lower due to a drier climate.

We also observed a parallel increase in the care seeking and content of perinatal care during the study period, but variable changes in the content of antenatal care. By the second wave of the IHOPE survey in 2016, the PIVOT-MoH partnership had been primarily focused on improving facility readiness and had not yet implemented specific clinical programs for maternal and reproductive health. In addition, while many health facility readiness programs started in mid-2014, the support to the community health worker program was only initiated in November 2015. This could explain why changes in sick-child care seeking at CHWs were marginal. Despite these limitations, the specific gaps observed between trends in care content and care seeking behavior highlight the fact that measures of care seeking are necessary but not sufficient to adequately evaluate the impact of HSS programs on delivering effective healthcare.

The high variability we found in the trends of care content across outputs examined at the local level is consistent with recent evidence observed at larger scales in studies comparing primary healthcare across several low-income countries [23,50,51]. Such analyses show that even among some populations with high coverage rates, large gaps in the content of care persist, resulting in inadequate management of patients [24,25,52,53]. Moreover, studies have found only weak correlations between care performance in low-income countries, facility infrastructure, and national wealth [26,50,54,55], suggesting that a focus on improving care content (i.e., by emphasizing consistent clinical assessment, adherence to protocols, respectful patient-provider interactions [56]) could achieve substantial improvements in care quality in these settings.

In the context of localized HSS impact studies, there has been limited use of content of care measures to explore care quality at the population level [7]. Content of care has most commonly been assessed by evaluating the practices of healthcare providers directly at health centers [57–59]. This method enables more detailed examination of services than is possible from population surveys (e.g., correct diagnosis, appropriate medicine dosage), but can introduce participation bias if providers and patients know they are being evaluated [16]. Moreover, using direct observational methods alone only accounts for people who reach the health facilities and precludes complementary measures of accessibility.

We also noted improvements in most measurements of service availability and readiness in the PIVOT-supported health centers. Within the first year of the intervention, all four PIVOT-supported health centers in the catchment area appeared to function close to full operational capacity, offering almost all preventative and therapeutic services, as well as becoming well supplied with basic health facility amenities and functional medical equipment. However, supply chain issues were pervasive and the provision of essential medicines remained at low levels in 2015 and decreased from 2014 levels. Medications for all health centers in the Ifanadiana district are ordered from a single regional distribution system; shortages of essential medicines in PIVOT-supported health centers are indicative of challenges in the supply chain keeping up with the increased demand, revealing a critical bottleneck in the healthcare delivery system that required improvement. SARA surveys conducted throughout Madagascar in 2014 indicate that about half of health centers lack stocks of zinc and oral rehydration therapy [60]. Moreover, similar data from multiple low-income countries reveal that the rate of essential medicines' availability is consistently low compared with other indicators measured in general service readiness [61].

Previous studies examining service readiness and availability in low- and middle-income countries have most commonly employed WHO's SARA tool or DHS and USAID's Service Provision Assessment (SPA) tool. Recently, researchers have also used the "clinical cascade" model to measure service-specific readiness, which organizes results hierarchically based on the order of variables necessary to sequentially identify, treat, and monitor or modify a particular health condition [62–64]. This methodology is clinically focused and less applicable to measures of general service readiness, which was the aim of this current study.

There were several limitations to this study. While we surveyed close to 1,600 households in each IHOPE survey, and over 400 children were reported to be ill within two weeks of each survey date, those children were separated into three groups based on symptoms in order to examine appropriate care, producing smaller sample sizes for each group. As a result, some estimates had large standard errors, which may explain, e.g., the minor apparent decreases observed in the non-intervention group despite the complementary health programs in place. In addition, data were based on self-reported answers from mothers, which could lead to lower estimates of illness or treatment if mothers did not recall the symptoms or treatments provided. Questions on content of medical care for childhood illnesses and maternal health were limited, as the IHOPE survey was largely based on the Malagasy DHS, making it

challenging to assess the appropriateness of certain drug prescriptions for individual patients. Complementing population-level surveys with direct observational surveys in health facilities, as discussed above, could help address questions of care appropriateness and issues of recall. Additionally, apparent increases in essential medications and basic equipment availability observed in the SARA survey could in part be attributable to either of the programs (PIVOT or PAUSENS) that strengthened health facilities evaluated. The lack of a control group in the SARA survey (only PIVOT-supported health centers were assessed) prevents us from isolating the effect of each program.

Regarding the study design, the IHOPE open longitudinal cohort confers some key advantages over multiple cross-sectional studies. In particular, a longitudinal study is a powerful way of controlling for the confounding effects of population and demographic changes through migration (i.e., it measures the effects of the intervention on the families and communities that were present at the beginning of the intervention). However, the cohort population can become less representative of the district population over time, and substantial loss to follow-up (which was not a substantial problem in the first two years of this study) can eventually limit analysis. For this reason, the IHOPE cohort replaces households unable or unwilling to participate in data collection with supplemental households from the original enumeration list (within the same cluster), which allows for some evolving representativeness of the population estimates. We also note that the intervention catchment area was not randomized across the district—it was a natural experiment in which study design followed the intervention, which was driven by practical considerations to strengthen the health system in alignment with the government. Although health seeking behaviors at baseline were similar between the two areas, some socioeconomic indicators were better within the intervention catchment than for the rest of the district, which could impact the results observed and limit our capacity to ensure that the parallel trends assumption was fulfilled. Nonetheless, we found that DiD estimates for all indicators were extremely similar when controlling for household wealth. Lastly, because clusters were based on geographic proximity, there is a risk for misclassification if people preferred to travel longer distances to attend an improved health center, which could underestimate the effect of the intervention.

Conclusion

Examining the rates of healthcare outputs at the population level, in addition to care seeking behavior, presents a more comprehensive picture of a program's impact on healthcare delivery. By controlling for baseline differences between the intervention group and the non-intervention group, we were able to identify areas of care that appeared to have significantly improved as a direct result of PIVOT-MoH's initiatives and those that still need improvement. As the PIVOT-MoH partnership continues to develop its clinical programs, particularly in maternal and reproductive health, we expect to observe a better match between the trends in healthcare seeking behavior and content of recommended care. This will be assessed in subsequent surveys of IHOPE's ongoing longitudinal cohort study. In addition, an expansion of health facility assessments is expected to provide complementary information on health system readiness across the Ifanadiana district. Together, this will help build an evidence base for the potential impact of integrated health systems strengthening interventions on the quality of care delivered in low-resource settings.

Supporting information

S1 Appendix. The file contains the following: A table of 10 essential components of high-quality health systems; a graphical representation of the DiD statistical calculation; a

figure of initiation and frequency of antenatal care attendance in the IHOPE cohort; additional information on the IHOPE cohort; and additional information on the SARA survey. DiD, difference-in-differences; IHOPE, The Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation; SARA, Service Availability and Readiness Assessment.
(DOCX)

S1 TIDIER Checklist. Summary of the HSS intervention carried out by PIVOT in Ifanadiana District between 2014 and 2016, based upon the TIDieR checklist. HSS, health system strengthening; TIDieR, Template for Intervention Description and Replication.
(DOCX)

S1 STROBE Checklist. The STROBE statement is a checklist of 22 items considered essential for good reporting of cohort studies. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.
(DOCX)

S1 Table. DiD estimates adjusted for household wealth. Table of DiD estimates and associated *p*-values for all indicators of sick-child, antenatal, and perinatal care assessed, comparing unadjusted and adjusted values after controlling for household wealth. DiD, difference-in-differences.
(XLSX)

S2 Table. Information on nonresponse rates in IHOPE survey. Table with rates of missing data for all indicators of sick-child, antenatal, and perinatal care assessed. IHOPE, The Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation.
(XLSX)

Acknowledgments

The authors thank Jim Herrnstein, Robin Herrnstein, Benjamin Andriamihaja, Lara Hall, Djordje Gikic, Amber Cripps, Pat Wright, and Paul Farmer for their assistance and contributions to this work. They also thank the field teams at Institut National de la Statistique (INSTAT) for their collaboration in the district-wide population survey. Finally, the authors are grateful to all the staff of PIVOT and the Ministry of Health for their support of the study and for their continued dedication to improving the health of Ifanadiana's population.

Author Contributions

Conceptualization: Camille Ezran, Matthew H. Bonds, Andres Garchitorena.

Data curation: Ann C. Miller, Laura F. Cordier, Justin Haruna, David Mwanawabenea, Marius Randriamanambintsoa, Hery-Tiana R. Razanadrakato, Mohammed Ali Ouenzar, Bénédicte R. Razafinjato.

Formal analysis: Camille Ezran, Laura F. Cordier.

Investigation: Matthew H. Bonds, Andres Garchitorena.

Methodology: Camille Ezran, Andres Garchitorena.

Software: Camille Ezran.

Supervision: Matthew H. Bonds, Andres Garchitorena.

Writing – original draft: Camille Ezran.

Writing – review & editing: Camille Ezran, Matthew H. Bonds, Ann C. Miller, Laura F. Cordier, Justin Haruna, David Mwanawabenea, Marius Randriamanambintsoa, Hery-Tiana R. Razanadrakato, Mohammed Ali Ouenzar, Bénédicte R. Razafinjato, Megan Murray, Andres Garchitorena.

References

1. The World Health Organization. Together on the road to universal health coverage, a call to action. 2017.
2. Lancet The. The Astana Declaration: the future of primary health care? Lancet. 2018; 392 (10156):1369. https://doi.org/10.1016/S0140-6736(18)32478-4 PMID: 30343840
3. The Alma-Ata 40 Roundtable. Implementing The Astana Declaration—What Alma-Ata Taught Us. Health Affairs Blog. 2018.
4. Global Burden of Disease Health Financing Collaborator Network. Trends in future health financing and coverage: future health spending and universal health coverage in 188 countries, 2016–40. Lancet. 2018; 391(10132):1783–98. https://doi.org/10.1016/S0140-6736(18)30697-4 PMID: 29678341
5. Stenberg K, Hanssen O, Edejer TT, Bertram M, Brindley C, Meshreky A, et al. Financing transformative health systems towards achievement of the health Sustainable Development Goals: a model for projected resource needs in 67 low-income and middle-income countries. The Lancet Global health. 2017; 5(9):e875–e87. https://doi.org/10.1016/S2214-109X(17)30263-2 PMID: 28728918
6. Global Burden of Disease 2016 Sustainable Development Goals Collaborators. Measuring progress and projecting attainment on the basis of past trends of the health-related Sustainable Development Goals in 188 countries: an analysis from the Global Burden of Disease Study 2016. Lancet. 2017; 390 (10100):1423–59. https://doi.org/10.1016/S0140-6736(17)32336-X PMID: 28916366
7. Thomson DR, Amoroso C, Atwood S, Bonds MH, Rwabukwisi FC, Drobac P, et al. Impact of a health system strengthening intervention on maternal and child health outputs and outcomes in rural Rwanda 2005–2010. BMJ global health. 2018; 3(2):e000674. https://doi.org/10.1136/bmjgh-2017-000674 PMID: 29662695
8. Liljestrand J, Sambath MR. Socio-economic improvements and health system strengthening of maternity care are contributing to maternal mortality reduction in Cambodia. Reproductive health matters. 2012; 20(39):62–72. https://doi.org/10.1016/S0968-8080(12)39620-1 PMID: 22789083
9. The World Health Organization. Everybody's business: strengthening health systems to improve health outcomes—WHO's framework for action. 2007.
10. Kruk ME, Gage AD, Arsenault C, Jordan K, Leslie HH, Roder-DeWan S, et al. High-quality health systems in the Sustainable Development Goals era: time for a revolution. The Lancet Global health. 2018; 6(11):e1196–e252. https://doi.org/10.1016/S2214-109X(18)30386-3 PMID: 30196093
11. Ng M, Misra A, Diwan V, Agnani M, Levin-Rector A, De Costa A. An assessment of the impact of the JSY cash transfer program on maternal mortality reduction in Madhya Pradesh, India. Global health action. 2014; 7:24939. https://doi.org/10.3402/gha.v7.24939 PMID: 25476929
12. Kruk ME, Larson E, Twum-Danso NA. Time for a quality revolution in global health. The Lancet Global health. 2016; 4(9):e594–6. https://doi.org/10.1016/S2214-109X(16)30131-0 PMID: 27539798
13. Loevinsohn B, Haq IU, Couffinhal A, Pande A. Contracting-in management to strengthen publicly financed primary health services—the experience of Punjab, Pakistan. Health policy. 2009; 91(1):17–23. https://doi.org/10.1016/j.healthpol.2008.10.015 PMID: 19070931
14. Akachi Y, Tarp F, Kelley E, Addisona T, Kruk ME. Measuring quality-of-care in the context of sustainable development goal 3: a call for papers. Bulletin of the World Health Organization. 2016; 94(3):160-A.
15. Leatherman S, Ferris TG, Berwick D, Omaswa F, Crisp N. The role of quality improvement in strengthening health systems in developing countries. International journal for quality in health care: journal of the International Society for Quality in Health Care. 2010; 22(4):237–43.
16. Peabody JW, Taguiwalo MM, Robalino DA, Frenk J. Improving the Quality of Care in Developing Countries. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al., editors. Disease Control Priorities in Developing Countries. 2nd ed. Washington (DC)2006.
17. Persson LA. Bridging the quality chasm in maternal, newborn, and child healthcare in low- and middle-income countries. PLoS Med. 2017; 14(12):e1002465. https://doi.org/10.1371/journal.pmed.1002465 PMID: 29232389

18. Ng M, Fullman N, Dieleman JL, Flaxman AD, Murray CJ, Lim SS. Effective coverage: a metric for monitoring Universal Health Coverage. PLoS Med. 2014; 11(9):e1001730. https://doi.org/10.1371/journal.pmed.1001730 PMID: 25243780

19. Kruk ME, Freedman LP. Assessing health system performance in developing countries: a review of the literature. Health policy. 2008; 85(3):263–76. https://doi.org/10.1016/j.healthpol.2007.09.003 PMID: 17931736

20. Hirschhorn LR, Baynes C, Sherr K, Chintu N, Awoonor-Williams JK, Finnegan K, et al. Approaches to ensuring and improving quality in the context of health system strengthening: a cross-site analysis of the five African Health Initiative Partnership programs. BMC health services research. 2013; 13 Suppl 2:S8.

21. Mitchell S, Gelman A, Ross R, Chen J, Bari S, Huynh UK, et al. The Millennium Villages Project: a retrospective, observational, endline evaluation. The Lancet Global health. 2018; 6(5):e500–e13. https://doi.org/10.1016/S2214-109X(18)30065-2 PMID: 29653625

22. Adam T, Hsu J, de Savigny D, Lavis JN, Rottingen JA, Bennett S. Evaluating health systems strengthening interventions in low-income and middle-income countries: are we asking the right questions? Health policy and planning. 2012; 27 Suppl 4:iv9–19.

23. Kruk ME, Gage AD, Mbaruku GM, Leslie HH. Content of Care in 15,000 Sick Child Consultations in Nine Lower-Income Countries. Health services research. 2018.

24. Benova L, Tuncalp O, Moran AC, Campbell OMR. Not just a number: examining coverage and content of antenatal care in low-income and middle-income countries. BMJ global health. 2018; 3(2):e000779. https://doi.org/10.1136/bmjgh-2018-000779 PMID: 29662698

25. Carvajal-Aguirre L, Amouzou A, Mehra V, Ziqi M, Zaka N, Newby H. Gap between contact and content in maternal and newborn care: An analysis of data from 20 countries in sub-Saharan Africa. Journal of global health. 2017; 7(2):020501. https://doi.org/10.7189/jogh.07.020501 PMID: 29423178

26. Koulidiati JL, Nesbitt RC, Ouedraogo N, Hien H, Robyn PJ, Compaore P, et al. Measuring effective coverage of curative child health services in rural Burkina Faso: a cross-sectional study. BMJ Open. 2018; 8(5):e020423. https://doi.org/10.1136/bmjopen-2017-020423 PMID: 29858415

27. The International Monetary Fund. World Economic Outlook Database 2018 [cited 15 Jul 2019] [Available from: http://www.imf.org/external/datamapper/datasets/WEO.

28. The World Health Organization. Global Health Observatory Data Repository 2018 [cited 15 Jul 2019] [Available from: http://www.who.int/gho/en/.

29. The World Health Organization. A Universal Truth: No Health Without a Workforce. 2014.

30. Institut Nationale des Statistiques Madagascar. Enquête Nationale Sur Le Suivi Des Objectifs Du Millénaire Pour Le Développement À Madagascar. 2013.

31. Miller AC, Ramananjato RH, Garchitorena A, Rabeza VR, Gikic D, Cripps A, et al. Baseline population health conditions ahead of a health system strengthening program in rural Madagascar. Global health action. 2017; 10(1):1329961. https://doi.org/10.1080/16549716.2017.1329961 PMID: 28621206

32. Bonds M, Garchitorena A, Cordier L, Miller AC, McCarty M, Andriamihaja B, et al. Advancing A Science For Sustaining Health: Establishing A Model Health District in Madagascar. bioRxiv. 2017.

33. Garchitorena A, Miller AC, Cordier LF, Rabeza VR, Randriamanambintsoa M, Razanadrakato HR, et al. Early changes in intervention coverage and mortality rates following the implementation of an integrated health system intervention in Madagascar. BMJ global health. 2018; 3(3):e000762. https://doi.org/10.1136/bmjgh-2018-000762 PMID: 29915670

34. Miller AC, Garchitorena A, Rabeza V, Randriamanambintsoa M, Rahaniraka Razanadrakato HT, Cordier L, et al. Cohort Profile: Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation (IHOPE). International journal of epidemiology. 2018.

35. Gulmezoglu AM, Lawrie TA, Hezelgrave N, Oladapo OT, Souza JP, Gielen M, et al. Interventions to Reduce Maternal and Newborn Morbidity and Mortality. In: Black RE, Laxminarayan R, Temmerman M, Walker N, editors. Reproductive, Maternal, Newborn, and Child Health: Disease Control Priorities, Third Edition (Volume 2). Washington (DC)2016.

36. Bishai DM, Cohen R, Alfonso YN, Adam T, Kuruvilla S, Schweitzer J. Factors Contributing to Maternal and Child Mortality Reductions in 146 Low- and Middle-Income Countries between 1990 and 2010. PLoS ONE. 2016; 11(1):e0144908. https://doi.org/10.1371/journal.pone.0144908 PMID: 26783759

37. Sheffel A, Karp C, Creanga AA. Use of Service Provision Assessments and Service Availability and Readiness Assessments for monitoring quality of maternal and newborn health services in low-income and middle-income countries. BMJ global health. 2018; 3(6):e001011. https://doi.org/10.1136/bmjgh-2018-001011 PMID: 30555726

38. Garchitorena A, Miller AC, Cordier LF, Ramananjato R, Rabeza VR, Murray M, et al. In Madagascar, Use Of Health Care Services Increased When Fees Were Removed: Lessons For Universal Health

Coverage. Health affairs. 2017; 36(8):1443–51. https://doi.org/10.1377/hlthaff.2016.1419 PMID: 28784737

39. The World Health Organization. Integrated Management of Childhood Illness—Chart Booklet. 2014.
40. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014; 348:g1687. https://doi.org/10.1136/bmj.g1687 PMID: 24609605
41. The World Bank. Madagascar—Emergency Support to Critical Education, Health, and Nutrition Services Project 2018 [cited 25 Jul 2019] [Available from: http://projects.worldbank.org/P131945/madagascar-emergency-support-critical-education-health-nutrition-services-project?lang=en.
42. USAID. USAID Mikolo 2018 [cited 25 Jul 2019] [Available from: https://www.msh.org/our-work/projects/usaid-mikolo.
43. Institut National de la Statistique—INSTAT/Madagascar, ICF Macro. Madagascar enquête démographique et de santé 2008–2009. Antananarivo, Madagascar: INSTAT and ICF Macro; 2010.
44. The World Health Organization. Service Availability and Readiness Assessment (SARA): An annual monitoring system for service delivery—Reference Manual. 2013.
45. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med. 2007; 4(10):e297. https://doi.org/10.1371/journal.pmed.0040297 PMID: 17941715
46. The World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. 2016.
47. The World Health Organization. Standards for improving quality of maternal and newborn care in health facilities. 2016.
48. The United States Agency for International Development. Making the Demographic and Health Surveys Wealth Index Comparable. DHS Methodological Reports No 9. 2014.
49. Kruk ME, Gage AD, Joseph NT, Danaei G, Garcia-Saiso S, Salomon JA. Mortality due to low-quality health systems in the universal health coverage era: a systematic analysis of amenable deaths in 137 countries. Lancet. 2018.
50. Kruk ME, Chukwuma A, Mbaruku G, Leslie HH. Variation in quality of primary-care services in Kenya, Malawi, Namibia, Rwanda, Senegal, Uganda and the United Republic of Tanzania. Bulletin of the World Health Organization. 2017; 95(6):408–18. https://doi.org/10.2471/BLT.16.175869 PMID: 28603307
51. Boonstra E, Lindbaek M, Ngome E. Adherence to management guidelines in acute respiratory infections and diarrhoea in children under 5 years old in primary health care in Botswana. International journal for quality in health care: journal of the International Society for Quality in Health Care. 2005; 17 (3):221–7.
52. Owolabi OO, Wong KLM, Dennis ML, Radovich E, Cavallaro FL, Lynch CA, et al. Comparing the use and content of antenatal care in adolescent and older first-time mothers in 13 countries of west Africa: a cross-sectional analysis of Demographic and Health Surveys. The Lancet Child & Adolescent Health. 2017; 1(3):203–12.
53. Arsenault C, Jordan K, Lee D, Dinsa G, Manzi F, Marchant T, et al. Equity in antenatal care quality: an analysis of 91 national household surveys. The Lancet Global health. 2018; 6(11):e1186–e95. https://doi.org/10.1016/S2214-109X(18)30389-9 PMID: 30322649
54. Leslie HH, Sun Z, Kruk ME. Association between infrastructure and observed quality of care in 4 healthcare services: A cross-sectional study of 4,300 facilities in 8 countries. PLoS Med. 2017; 14(12): e1002464. https://doi.org/10.1371/journal.pmed.1002464 PMID: 29232377
55. Fernandes QF, Wagenaar BH, Anselmi L, Pfeiffer J, Gloyd S, Sherr K. Effects of health-system strengthening on under-5, infant, and neonatal mortality: 11-year provincial-level time-series analyses in Mozambique. The Lancet Global health. 2014; 2(8):e468–77. https://doi.org/10.1016/S2214-109X(14)70276-1 PMID: 25103520
56. Austad K, Chary A, Martinez B, Juarez M, Martin YJ, Ixen EC, et al. Obstetric care navigation: a new approach to promote respectful maternity care and overcome barriers to safe motherhood. Reprod Health. 2017; 14(1):148. https://doi.org/10.1186/s12978-017-0410-6 PMID: 29132431
57. Pariyo GW, Gouws E, Bryce J, Burnham G, Uganda IIST. Improving facility-based care for sick children in Uganda: training is not enough. Health policy and planning. 2005; 20 Suppl 1:i58–i68.
58. Bryce J, Gouws E, Adam T, Black RE, Schellenberg JA, Manzi F, et al. Improving quality and efficiency of facility-based child health care through Integrated Management of Childhood Illness in Tanzania. Health policy and planning. 2005; 20 Suppl 1:i69–i76.
59. Youngleson MS, Nkurunziza P, Jennings K, Arendse J, Mate KS, Barker P. Improving a mother to child HIV transmission programme through health system redesign: quality improvement, protocol

adjustment and resource addition. PLoS ONE. 2010; 5(11):e13891. https://doi.org/10.1371/journal.pone.0013891 PMID: 21085479

60. Andriantsimietry SH, Rakotomanga R, Rakotovao JP, Ramiandrison E, Razakariasy MER, Favero R, et al. Service Availability and Readiness Assessment of Maternal, Newborn and Child Health Services at Public Health Facilities in Madagascar. African journal of reproductive health. 2016; 20(3):149–58. PMID: 29553204

61. O'Neill K, Takane M, Sheffel A, Abou-Zahr C, Boerma T. Monitoring service delivery for universal health coverage: the Service Availability and Readiness Assessment. Bulletin of the World Health Organization. 2013; 91(12):923–31. https://doi.org/10.2471/BLT.12.116798 PMID: 24347731

62. Church K, Machiyama K, Todd J, Njamwea B, Mwangome M, Hosegood V, et al. Identifying gaps in HIV service delivery across the diagnosis-to-treatment cascade: findings from health facility surveys in six sub-Saharan countries. J Int AIDS Soc. 2017; 20(1):21188. https://doi.org/10.7448/IAS.20.1.21188 PMID: 28364566

63. Cranmer JN, Dettinger J, Calkins K, Kibore M, Gachuno O, Walker D. Beyond signal functions in global obstetric care: Using a clinical cascade to measure emergency obstetric readiness. PLoS ONE. 2018; 13(2):e0184252. https://doi.org/10.1371/journal.pone.0184252 PMID: 29474397

64. Morgan MC, Spindler H, Nambuya H, Nalwa GM, Namazzi G, Waiswa P, et al. Clinical cascades as a novel way to assess physical readiness of facilities for the care of small and sick neonates in Kenya and Uganda. PLoS ONE. 2018; 13(11):e0207156. https://doi.org/10.1371/journal.pone.0207156 PMID: 30462671

Health Policy and Planning, **00**, 2021, 1–12
DOI: https://doi.org/10.1093/heapol/czab087
Original Article

Geographic barriers to achieving universal health coverage: evidence from rural Madagascar

Andres Garchitorena[1,2,*], Felana A Ihantamalala[2], Christophe Révillion[3], Laura F Cordier[2], Mauricianot Randriamihaja[2,4], Benedicte Razafinjato[2], Feno H Rafenoarivamalala[2], Karen E Finnegan[2,5], Jean Claude Andrianirinarison[6,7], Julio Rakotonirina[6,8], Vincent Herbreteau[9] and Matthew H Bonds[2,5]

[1]MIVEGEC, University Montpellier, CNRS, IRD, 911 Avenue Agropolis, 34394 Montpellier, Montpellier, France
[2]NGO PIVOT, BP23 Ranomafana, 312 Ifanadiana, Madagascar
[3]Université de La Réunion, UMR 228 Espace-Dev (IRD, UA, UG, UM, UR), 40 Av De Soweto, 97410 Saint-Pierre, Réunion, France
[4]School of Management and Technological innovation, University of Fianarantsoa, BP 1135 Andrainjato, 301 Fianarantsoa, Madagascar
[5]Department of Global Health and Social Medicine, Harvard Medical School, 641 Huntington Avenue, Boston, Massachusetts 02115, USA
[6]Ministry of Public Health, Ambohidahy, 101 Antananarivo, Madagascar
[7]National Institut of Public Health, Befelatanana, 101 Antananarivo, Madagascar
[8]Faculty of Medicine, BP. 375, 101 Antananarivo, Madagascar
[9]Institut de Recherche pour le Développement, UMR 228 Espace-Dev (IRD, UA, UG, UM, UR), B.P. 86, Phnom Penh, Cambodia

*Corresponding author. Institut de Recherche pour le Développement, UMR MIVEGEC, 911 Avenue Agropolis, Montpellier 34394, France.
E-mail: andres.garchitorena@gmail.com

Accepted on 16 July 2021

Abstract

Poor geographic access can persist even when affordable and well-functioning health systems are in place, limiting efforts for universal health coverage (UHC). It is unclear how to balance support for health facilities and community health workers in UHC national strategies. The goal of this study was to evaluate how a health system strengthening (HSS) intervention aimed towards UHC affected the geographic access to primary care in a rural district of Madagascar. For this, we collected the fokontany of residence (lowest administrative unit) from nearly 300 000 outpatient consultations occurring in facilities of Ifanadiana district in 2014–2017 and in the subset of community sites supported by the HSS intervention. Distance from patients to facilities was accurately estimated following a full mapping of the district's footpaths and residential areas. We modelled per capita utilization for each fokontany through interrupted time-series analyses with control groups, accounting for non-linear relationships with distance and travel time among other factors, and we predicted facility utilization across the district under a scenario with and without HSS. Finally, we compared geographic trends in primary care when combining utilization at health facilities and community sites. We find that facility-based interventions similar to those in UHC strategies achieved high utilization rates of 1–3 consultations per person year only among populations living in close proximity to facilities. We predict that scaling only facility-based HSS programmes would result in large gaps in access, with over 75% of the population unable to reach one consultation per person year. Community health delivery, available only for children under 5 years, provided major improvements in service utilization regardless of their distance from facilities, contributing to 90% of primary care consultations in remote populations. Our results reveal the geographic limits of current UHC strategies and highlight the need to invest on professionalized community health programmes with larger scopes of service.

Keywords: Community health, geographical information systems, healthcare utilization, health systems research, inequality

Introduction

Despite considerable progress on the health-related development goals, every year five million children under 5 years die of treatable illnesses such as malaria, diarrhoea and respiratory infections. More than three and a half billion people lack access to essential health services (The World Bank, 2017; Fullman *et al.*, 2017). At the recent 40-year anniversary of the Alma Ata Declaration, 134 countries signed on to a renewed commitment to universal health coverage (UHC) based on a shared vision that primary health care and health services be 'high quality, safe, comprehensive, integrated, accessible, available, and affordable for everyone everywhere' (World Health Organization, 2018a). In practice, UHC policies tend to focus on financial coverage, such as through health insurance, in order to reduce out-of-pocket payments at health facilities, which are known to be barriers to care (Sachs, 2012; Garchitorena *et al.*, 2017; Dhillon *et al.*, 2011; Langlois *et al.*, 2016; Zombré *et al.*, 2017; Lagarde and Palmer, 2011; Johri *et al.*, 2014). However, there is growing recognition that among the greatest challenges to accessing health care are geographic barriers: terrain, waterways and other factors associated with physical distance between the patient and the service (Feikin *et al.*, 2009; McLaren *et al.*, 2014; Gething *et al.*, 2012; Noor *et al.*, 2003; Stock, 2012). The use of primary care decreases exponentially for populations living at increasing distance of primary healthcare centres (PHCs),

Key messages

- Limited geographic access to primary care is one of the most important and hardest challenges for achieving UHC and improving population health in developing countries.
- There is little evidence on how health system change linked to UHC affects the geography of health access, leaving open questions about their effects on remote populations.
- We combined geographic data from hundreds of thousands of patient records from a rural district's health system to identify the impact of a HSS intervention on geographic trends in access to care.
- Our results provide evidence of the substantial gaps in care that persist unless health systems integrate professional community health programmes with an expanded scope of services.

known as the 'distance decay' effect (Feikin *et al.*, 2009; McLaren *et al.*, 2014; Gething *et al.*, 2012; Noor *et al.*, 2003; Stock, 2012). Distance decay in health access is equivalent to the effect of user fees (Bates *et al.*, 2012), which can be more directly reduced or eliminated (Sachs, 2012; Garchitorena *et al.*, 2017; Dhillon *et al.*, 2011; Langlois *et al.*, 2016; Zombré *et al.*, 2017; Lagarde and Palmer, 2011; Johri *et al.*, 2014).

While there is a considerable body of evidence on the relationship between health system access and user fees, there is surprisingly little evidence on the relationship between health system change and the geography of health access. Studies suggest that geographic barriers to PHC persist even when user fees have been removed, making these approaches insufficient to reach full population coverage of primary care services (Nguyen *et al.*, 2018; De Allegri *et al.*, 2011; Mills *et al.*, 2008). The leading policy strategy for addressing geographic barriers is through community health workers (CHWs); i.e. lay people who are trained to treat a subset of clinical cases (World Health Organization, 2018b; 2010). Yet, little is known about the effects of community health systems on the geography of health access or about their contribution towards the realization of universal access to primary health care. Can the leading policies designed to improve healthcare coverage—UHC and community health—actually overcome these key barriers?

In most developing countries, national policies consider CHWs as local volunteers, with minimum requirements of formal education. Compensation for CHWs is well below the national minimum wage and is frequently based on a social marketing strategy, where CHWs earn a markup for the sale of medicines. Community-based diagnosis and treatment is generally restricted to malaria, pneumonia and diarrhoea for children under five (Ahmed *et al.*, 2010). The burden of disease thus remains unmet for the large majority of the population, even when community health systems are fully functioning. New World Health Organization (WHO) guidelines, not yet fully adopted by most countries, recommends paying CHWs minimum wage, removing use fees and providing dedicated supervision (World Health Organization, 2018b), but there remains debate on how to optimize community health.

The situation of Madagascar is illustrative of the challenges of many low-income countries attempting to translate international policies for UHC and community health to the national level in a context of limited resources. This island nation is one of the poorest countries in the world, with among the least well-funded health systems (World Bank, 2019). In 2014, Madagascar had less than three doctors, nurses and midwives per 10 000 people (World Health Organization, 2019), with a lower concentration in rural areas, where over three-quarters of the population live (Institut National de la Statistique, 2009). Access to health care is particularly low for the majority of the population living more than 5 km away from a PHC (Garchitorena *et al.*, 2017; World Health Organization, 2019; Kashima *et al.*, 2012). To address this, the country has significantly increased health spending in recent years and, in 2015, it signed a national policy for UHC that is currently in its pilot phase (Government of Madagascar, 2015). Yet, the contribution of CHWs to improving primary care access in Madagascar is limited, since CHWs work on a voluntary basis, manage mostly illnesses of early childhood, and significant challenges remain to support their activities (e.g. supervision and procurement).

Here, we take advantage of a natural experiment in global health, where an integrated, district-level health system strengthening (HSS) intervention aimed at achieving universal coverage at the local level was implemented in a rural district of Madagascar, ahead of the national scale up of the UHC strategy. Starting in 2014, a non-governmental organization (NGO), partnered with the Government of Madagascar to establish a model health system in the southeastern district of Ifanadiana (~200 000 people). A range of HSS programmes were initiated in a third of the district (see Supplementary Table S1), removing user fees at health facilities, ensuring health system readiness (infrastructure, personnel and supply chain), improving clinical programmes (maternal and child health) and supporting integrated information systems at all levels of care (community health, primary care facilities and the district hospital). Early results showed improved quality of primary care (Ezran *et al.*, 2019), a tripling of facility utilization rates (Garchitorena *et al.*, 2018), and declines in under-five and infant mortality rates in the first 2 years of intervention (Garchitorena *et al.*, 2018). Later, in 2016, these programmes were extended to include strengthened CHWs—who were trained, supervised and equipped (Cordier *et al.*, 2020; Bonds *et al.*, 2017).

With a unique geographically explicit patient-level data set encompassing all health centre visits in the district during 4 years, the aim of this study was to examine the effect of increasing financial coverage and strengthening the public health system on the geographic access (community *vs* facility-based) to primary health care. The ultimate goal was to provide evidence, via this district-level pilot, on the contribution and limitations of broader policies for UHC and community health towards the realization of universal access to primary health care in rural settings of developing countries.

Methods

Study site

Ifanadiana is a rural health district of approximately 200 000 people located in the region of Vatovavy-Fitovinany, in Southeastern Madagascar. As per Ministry of Health (MoH) norms, Ifanadiana district has one reference hospital, one main primary care health centre (PHC2) for each of its

13 communes (subdivision of a district with ~15 000 people), six additional basic health centres for its larger communes (PHC1), and one community health site with two CHWs for each of its 195 fokontany (subdivision of a commune with ~1000 population). The integrated HSS intervention carried out by the MoH–NGO partnership (summarized in Supplementary Table S1) began in 2014, is guided by existing MoH policies, covers all six WHO building blocks of HSS and is implemented across all three levels of care in the district (community, health centre and hospital). This intervention is structured through the integration of horizontal improvements in system 'readiness', vertically aligned clinical programmes and information systems. Readiness includes infrastructure and sanitation, staffing and equipment to improve the quality of care; procurement systems; an ambulance network; the removal of user fees and provision of social support to patients; trainings and frequent supervision of health staff. The clinical programmes include malnutrition and integrated management of child illness through strengthened community health programmes, PHCs and hospital (details can be found in Garchitorena *et al.*, 2018; Bonds *et al.*, 2017). The core activities in the first years (2014–2017) covered approximately one-third of the population of Ifanadiana (referred to as 'HSS catchment'), with some activities such as medical staff recruitments spanning the whole district (Supplementary Table S1).

In addition to the HSS intervention, the population of Ifanadiana benefited from two other notable programmes that covered both the HSS catchment and the rest of the district (RoD) in this period. The PAUSENS project, funded by the World Bank and implemented in 2013–2017, provided a basic package of services free of charge in all 13 PHC2 for every woman attending the health centre for antenatal, delivery or postnatal care (first 6 weeks) and children under age five with any illness (The World Bank, 2012). The project also included training, support for child vaccination in remote areas and some equipment to health centres. The Mikolo project, funded by U.S. Agency for International Development and implemented in 2012–2017, provided support to a network of 150 CHWs in the remote fokontany (further than 5 km from a health centre) of eight communes in Ifanadiana, four of which were in the HSS catchment and four in RoD. The project organized annual trainings and periodic supervision and provided some equipment, supplies and an initial stock of medicines to each CHWs. The main difference between HSS catchment and RoD (our control group) was the implementation of the HSS intervention by the MoH–NGO partnership.

Health system utilization data

From January 2014 to December 2017, we obtained data from the registries on all individuals attending any PHC for an outpatient consultation in the district. The data were collected via regular visits to each PHC in the district by the NGO staff every 3–4 months, in agreement with the head of each PHC and the district medical inspector. This allowed for the creation of a patient-level, de-identified digital database. For each patient (new visits; follow-up excluded), information included the age, name of the fokontany of residence and malaria status. Fokontany are the smallest administrative units, composed of one or several villages, and are located at varying distances from the nearest PHC (0–20 km). For the period from January to December 2017, we also collected consultation data from the community health sites supported by the MoH–NGO partnership at this time (four out of five communes in the intervention area and 43 fokontany with an estimated population of about 55 000). This information, which was already available at the fokontany level, was obtained from the monthly report to the district and was verified for data quality and corrected where necessary by the NGO's monitoring and evaluation team.

Population data for each fokontany was obtained from the MoH. Consistent with MoH estimates, the population of children under 5 years was set at 18% of the total catchment population. Although official population data are sometimes deemed inaccurate, we previously showed that estimating catchment populations using available data for our district from other recognized sources such as WorldPop (2017) did not change the results of per capita utilization rates analyses (Garchitorena *et al.*, 2017). Information about key dates of the HSS intervention, especially the beginning of the user-fee exemption programme and the community health programme for each supported commune, were obtained from internal records within the NGO. Number of health professionals at each PHC per month were obtained from district's records and Service Availability and Readiness Assessments (Ezran *et al.*, 2019).

Geographic information system

We gathered geographic information from multiple sources in order to estimate the distance and travel time from each house in Ifanadiana district to the nearest PHC. First, we mapped all footpaths, residential areas, houses and rice fields in the district using very-high-resolution satellite images available through OpenStreetMap (OSM). For this, we implemented a participatory approach in collaboration with the non-profit organization Humanitarian OpenStreetMap Team (HOT). The district was divided in tiles of 1 km by 1 km and a request for mapping them was made publicly available through the HOT website (Humanitarian OpenStreetMap Team, 2019). Mapping was carried out in a two-stage process, where tiles that had been mapped had to be validated by a separate contributor. Most tiles were mapped and validated by a dedicated team hired through the project to ensure data quality and completion within the project deadlines. When mapping was completed, we used the Open Source Routing Machine (OSRM) engine to query our OSM data and accurately estimate the shortest path between each house in the district and the nearest PHC.

Second, to estimate travel speed by foot under different terrain and environmental conditions, we conducted field global positioning system (GPS) tracking between September 2018 and April 2019 in a sample of itineraries in Ifanadiana. A total of 168 itineraries by foot amounting to nearly 1000 km were collected by the NGO's community and research teams, in collaboration with CHWs. For this, we used the android mobile app 'OSMAnd' installed in tablets (Samsung Galaxy A10.1) and we recorded every 10 s the GPS coordinates, time and altitude.

Third, we built remotely sensed land cover maps combining information from Sentinel-2 satellites and OSM. We integrated land cover maps with the rest of graphical information system (GIS) data (climate, elevation, etc.) to statistically model travel speed and estimate terrain characteristics

associated with higher or lower speed using a generalized additive mixed model. We finally combined model results, GIS data and the shortest paths estimated by OSRM in order to predict travel time to seek care at the nearest PHC for every house in Ifanadiana. The aggregated distance and travel time for a fokontany was the average of all houses in the fokontany. A detailed description of the methods used to estimate distance and travel time to PHC is available in Ihantamalala *et al.* (2020).

Data analysis of health system data

The impact of the HSS intervention on utilization rates at each fokontany was modelled using interrupted time-series analyses with control groups (Kontopantelis *et al.*, 2015). For this, we first aggregated health centre patient-level information to estimate per capita utilization rates per month for each Fokontany in Ifanadiana district (Figure 1). We studied the linear and non-linear effect of travel distance and travel time from each fokontany to the nearest PHC on utilization rates. We assessed the impact of two programmes designed to reduce financial barriers (i.e. user-fee exemption) and to reduce geographic barriers (i.e. community programme) by assessing the level of change in utilization (immediate impact) associated with each programme (Kontopantelis *et al.*, 2015). We hypothesized that the community programme could have a positive impact on facility-based PHC utilization via increased sensitization, awareness and referrals by CHWs, especially for the 82% of the population over 5 years of age that is beyond the scope of CHWs work. We also controlled for linear and seasonal trends in utilization rates in the absence of the programmes; for baseline differences in HSS-supported PHC and in the type of PHC (PHC1 or PCH2); and for the number of health staff over time in the closest PHC for each fokontany.

Per capita utilization rates at PHC were modelled for each fokontany using binomial regressions in generalized linear mixed models, with a random intercept introduced for the closest PHC. All other variables were introduced as fixed effects. Each explanatory variable was studied through univariate analyses and those with *P*-values below 0.1 were included in multivariate models. Orthogonal polynomial terms of degree 2 were included to account for the non-linear relationship of per capita utilization with travel distance/time to the PHC. We included interaction terms between the HSS programmes and the travel distance/time to the PHC in the multivariate model to test whether these programmes had a different effect on remote populations. Model selection was performed through step-wise procedures based on Akaike information criterion (AIC), by selecting the reduced model with the lowest AIC. Model assumptions in the final model were verified, including violations to homogeneity and independence of residuals. We introduced a 1-month utilization lag in the final models to remove temporal autocorrelation in the residuals. To facilitate interpretation of results, we report exponentiated model coefficients, which reflect the ratio of change (odds ratio, OR) in utilization rates associated with each explanatory variable. Several sets of analyses were carried out in order to study PHC utilization separately in the general population, in specific age groups (children under five), and including or excluding malaria cases from the analyses. Using the final model for the general population, we predicted PHC utilization for every Fokontany in Ifanadiana under a scenario without HSS programmes (no user-fee

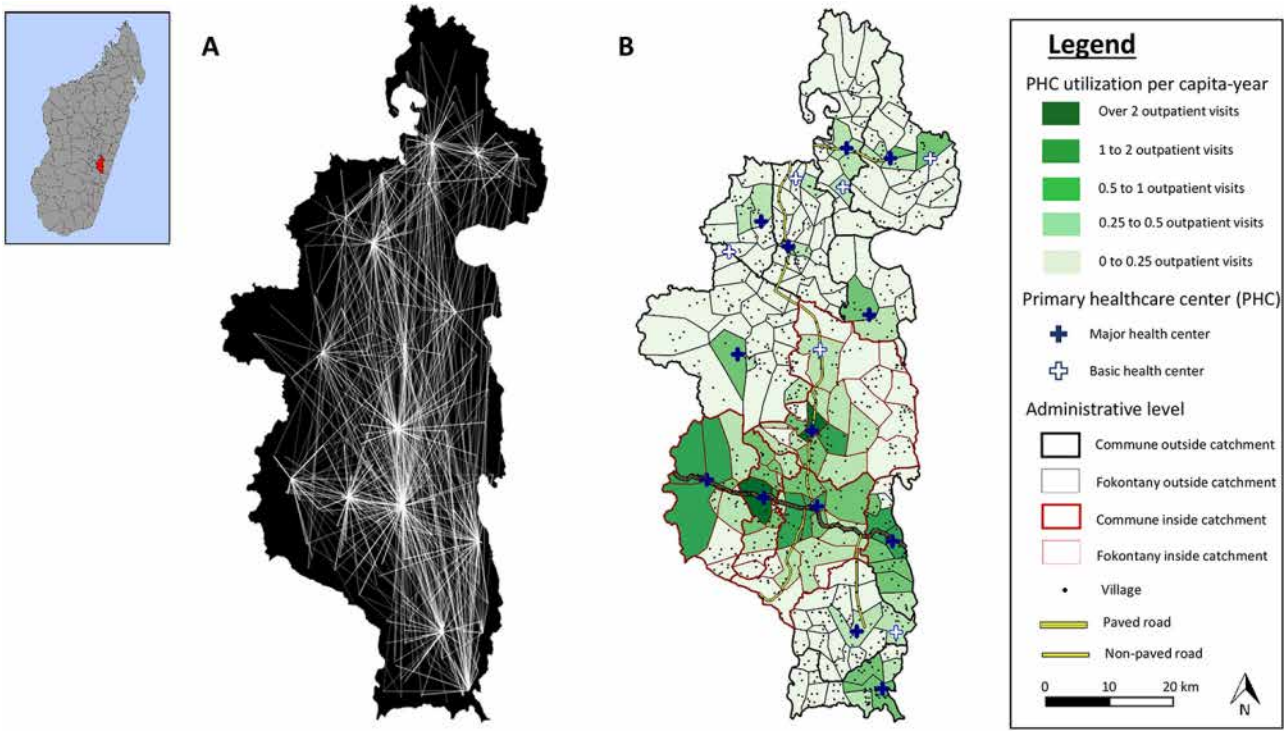

Figure 1. Geographic origin of patients from the 19 PCH in Ifanadiana district, 2014–2017. (A) Origin of all patients attending each of the 19 health centers in Ifanadiana district. For improved visualization, lines between Fokontany and PHC are included only when they represent over 100 patients, with line transparency inversely proportional to the logarithm of the number of visits. These data were aggregated to obtain a total number of per-capita visits per month for each Fokontany (lowest administrative unit, comprising one or several villages). (B) Average number of PHC visits per capita-year for each Fokontany during the study period.

exemption, no community health support and three health staff per PHC) and with HSS programmes (user-fee exemption, community health support and seven health staff per PHC). Finally, we compared geographic trends in primary care when combining utilization at both PHC and community health sites in the subset of 43 fokontany where the community health programme had been strengthened by the MoH–NGO partnership. Analyses were performed with R software (R Development Core Team, 2011) and R packages 'lme4', 'gstat', 'rgdal' and 'ggplot2'.

Results

PHC utilization by geographic proximity

Of the 314 443 patients who attended a PHC for an outpatient visit, 276 865 patients had a known geographic location and 99.25% of these (274 798) came from within the district (Supplementary Figure S1). Table 1 presents summary statistics of the patient population based on these geographic analyses. Although more than two-thirds of the population lived further than 5 km from a PHC (5–22 km) and 27% lived further than 10 km (10–22 km), these populations represented only 40% and 9% of all patient visits, respectively. Only a fourth of the population lived within 1 h of a PHC. Average annual PHC utilization per capita rates were nearly triple inside the HSS intervention catchment (0.64) than in the RoD (0.23) for all ages and more than double for children under 5 years. Utilization rates more than halved for every 5 km and every hour of travel from a PHC for every age group considered (Table 1).

Spatial analyses revealed that utilization rates increased over time in the HSS intervention catchment but declined dramatically as distance increased within the first 5 km from a PHC, especially after the system was strengthened at the facility level (Figure 2). The HSS intervention exacerbated the impact of geography on utilization (Figure 2b and c), but the ratio in PHC utilization between populations living in close proximity (<2.5 km) *vs* those leaving the furthest (>10 km) remained the same at over 10 times higher. Following user-fee exemptions, the HSS intervention catchment experienced a substantial increase in utilization, from 1 to nearly 3 visits per capita year for populations living in close proximity to a PHC and from 0.25 to about 0.5 visits per capita year for populations living 5–10 km from a PHC (Figure 2b and c).

Despite strong seasonal variation in utilization rates, particularly for populations living close to a PHC, trends remained unchanged in the RoD during the study period (Figure 3). Compared with the RoD, HSS activities in the intervention catchment resulted in a shift by 5 km in PHC utilization patterns so that populations living 5 km further from a strengthened PHC accessed care at rates comparable to those living 5 km closer to a facility that did not receive the intervention (Figure 3). We also observed seasonality in the average distance patients travelled to access a PHC during the year (Supplementary Figure S2). Overall, 50% of outpatient visits seen in the intervention catchment came from localities within 2 km of a PHC and over 75% from localities within 4 km, but in the months of May through July (dry season) patients came from further away. These seasonal patterns were not observed in the RoD (Supplementary Figure S2).

Table 1. Geographic distribution of populations and PHC outpatient visits in Ifanadiana district, 2014–2017

		HSS Catchment		Distance to PHC			Time to PHC		
	District	Inside	RoD	0–5 km	5–10 km	10–22 km	0–1 h	1–2 h	2–5 h
Population (prop.)									
All ages	198 175	72 152 (0.36)	126 023 (0.64)	63 811 (0.32)	80 790 (0.41)	53 573 (0.27)	49 269 (0.25)	74 169 (0.37)	74 738 (0.38)
Under 5 years old	35 671	12 987 (0.36)	22 684 (0.64)	11 486 (0.32)	14 542 (0.41)	9643 (0.27)	8868 (0.25)	13 350 (0.37)	13 453 (0.38)
Over 5 years old	162 503	59 164 (0.36)	103 338 (0.64)	52 325 (0.32)	66 248 (0.41)	43 930 (0.27)	40 400 (0.25)	60 818 (0.37)	61 285 (0.38)
Total number of patients (prop.)									
All ages	270 747	173 497 (0.64)	97 250 (0.36)	163 656 (0.6)	83 667 (0.31)	23 424 (0.09)	145 249 (0.54)	83 154 (0.31)	42 344 (0.15)
Under 5 years old	92 533	52 240 (0.56)	40 293 (0.44)	52 761 (0.57)	31 308 (0.34)	8464 (0.09)	45 576 (0.49)	31 356 (0.34)	15 601 (0.17)
Over 5 years old	178 214	121 257 (0.68)	56 957 (0.32)	110 895 (0.62)	52 359 (0.29)	14 960 (0.08)	99 673 (0.56)	51 798 (0.29)	26 743 (0.15)
Per capita utilization per year									
All ages	0.39	0.64	0.23	0.74	0.29	0.12	0.84	0.32	0.16
Under 5 years old	0.74	1.07	0.53	1.33	0.6	0.25	1.46	0.67	0.33
Over 5 years old	0.31	0.54	0.16	0.61	0.22	0.1	0.70	0.24	0.12

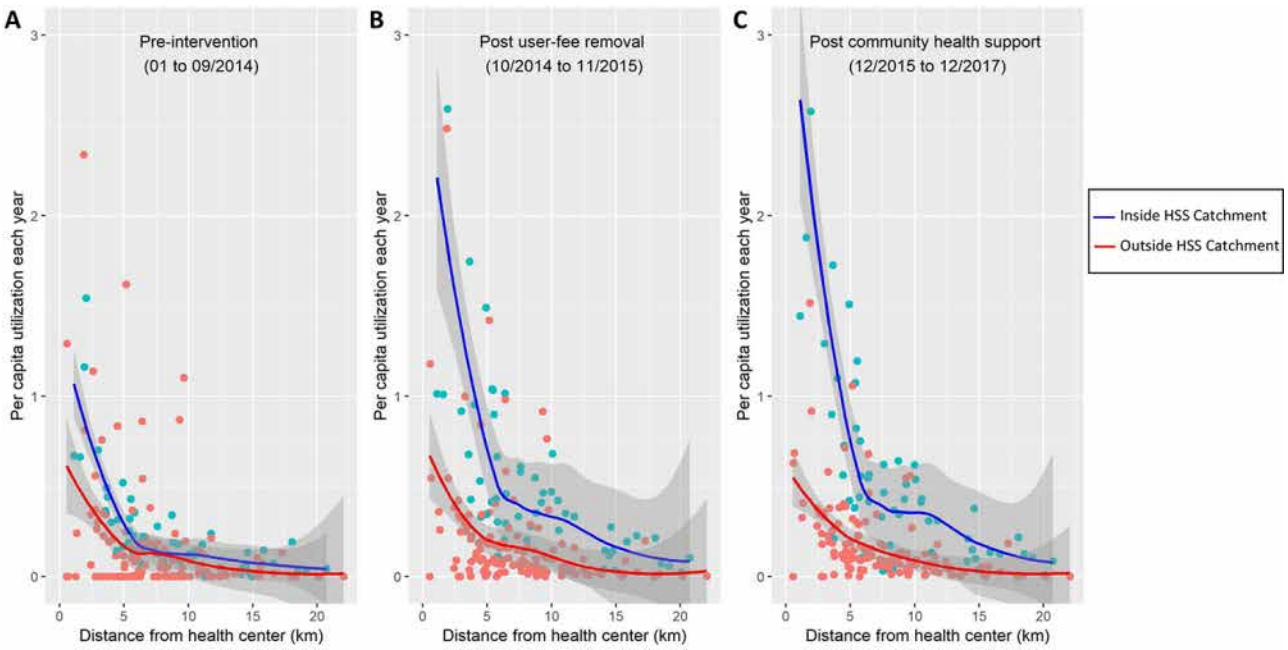

Figure 2. Average PHC per capita utilization by distance of Fokontany to PHC. Colors represent the HSS intervention catchment (blue) and the rest of Ifanadiana district (blue). Each dot represents one of the 195 Fokontany in Ifanadiana, solid lines are the respective non-linear smooth (local regression, LOESS method) and grey shades are the 95% confidence intervals around each smooth. A clear distance decay pattern can be observed, accentuated for the HSS intervention catchment due to a larger increase in utilization near PHC following the HSS intervention (B and C). To improve visualization, one dot from the HSS intervention catchment post intervention (4.5 per capita-year) was removed.

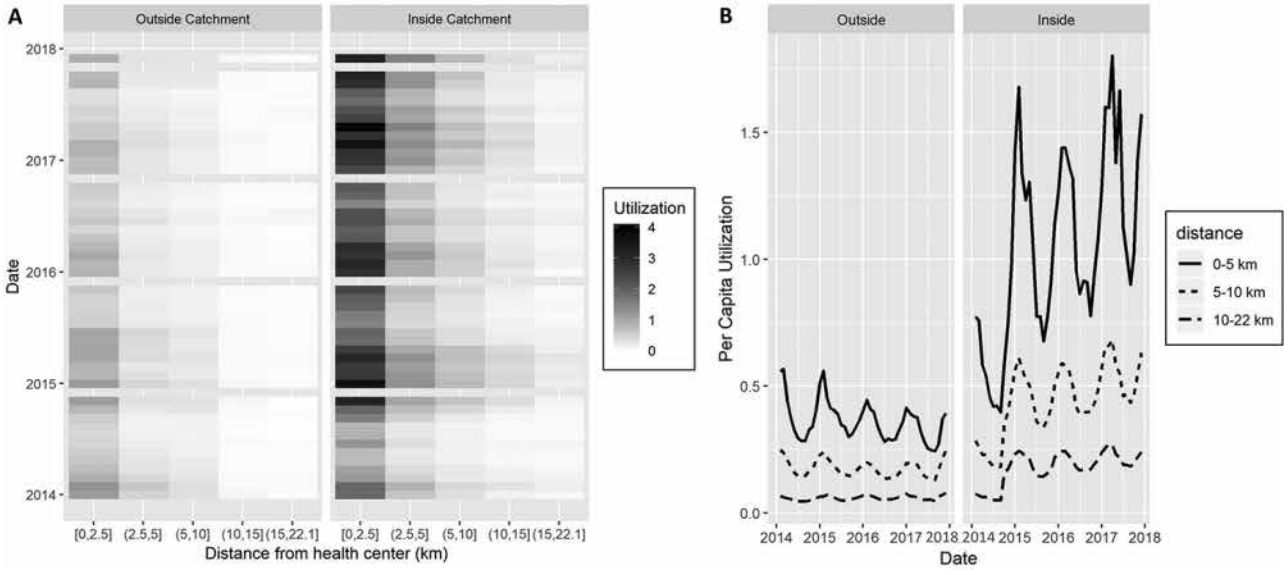

Figure 3. Time-series of PHC per capita utilization by distance of Fokontany to PHC, inside and outside the HSS intervention catchment. (A) Heat map of observed monthly PHC utilization, where grey color scale is proportional to average per capita values at each distance. (B) Model predictions of PHC per capita utilization for Ifanadiana, aggregated by intervention catchment area and distance to PHC. Both graphs show that implementation of HSS activities in the intervention catchment resulted in a shift by 5km of PHC utilization patterns (e.g. those living 5-10km from a PHC in the intervention catchment, have similar utilization rates than those within 5km outside the catchment). Utilization rates were annualized to improve comparability of results.

Impact of HSS programmes on PHC utilization

Our models confirmed the exponential decrease in PHC utilization due to geographic distance after accounting for programme implementation, health system factors and underlying temporal trends (Table 2, Supplementary Figure S3). We carried out several models to understand the consistency of associations when including or excluding malaria cases (because of their influence on PHC utilization seasonality), as well as for populations of all ages or only children under 5 years. In every model, a non-linear relationship with distance to PHC best explained utilization patterns (better than using a linear relationship with distance or using travel time as the explanatory variable), and this was the most important variable associated with PHC utilization trends

Table 2. Multivariate model results (generalized linear mixed models with random intercept at the PHC closest to the fokontany of residence)

Variable	Outpatient visits for all ages OR (95% CI)	Outpatient visits for children under age 5 OR (95% CI)	Outpatient visits for all ages, excluding malaria OR (95% CI)	Outpatient visits for children under age 5, excluding malaria OR (95% CI)
Intercept (visits per capita month)	0.02 (0.011–0.037)	0.032 (0.019–0.054)	0.015 (0.008–0.03)	0.024 (0.013–0.043)
Geographic factors				
Network distance to PHC (10 km, linear)[a]	0.126 (0.121–0.131)	0.228 (0.212–0.244)	0.095 (0.091–0.1)	0.141 (0.13–0.154)
Network distance to PHC (10 km, quadratic)[a]	1.102 (1.076–1.13)	0.898 (0.862–0.937)	1.261 (1.226–1.297)	1.07 (1.018–1.126)
Health system factors				
Number of health staff	1.042 (1.037–1.048)	1.032 (1.023–1.041)	1.043 (1.037–1.049)	1.039 (1.029–1.048)
Major PHC (*vs* basic PHC)	3.238 (1.5–6.993)	3.449 (1.764–6.744)	3.16 (1.421–7.024)	3.634 (1.762–7.493)
HSS catchment (*vs* outside)	0.663 (0.636–0.69)	0.637 (0.597–0.68)	0.641 (0.611–0.672)	0.634 (0.587–0.684)
Impact of HSS programmes				
User-fee exemption programme	1.09 (1.063–1.118)	0.946 (0.908–0.987)	1.18 (1.145–1.215)	–
Interaction with distance to PHC (10 km)[a]	1.454 (1.433–1.476)	1.416 (1.385–1.448)	1.44 (1.415–1.466)	1.361 (1.328–1.394)
Community health programme	1.147 (1.125–1.17)	1.148 (1.118–1.179)	1.112 (1.087–1.137)	1.081 (1.039–1.125)
Interaction with distance to PHC (10 km)[a]	1.095 (1.08–1.111)	–	1.127 (1.109–1.145)	1.052 (1.02–1.085)
Underlying trends				
Linear trend (year)	0.968 (0.962–0.973)	0.968 (0.959–0.977)	0.988 (0.981–0.995)	–
Seasonal trend[b]	1.204 (1.197–1.211)	1.212 (1.199–1.225)	1.031 (1.024–1.038)	1.127 (1.114–1.141)
Lagged trend (1-month lag)[c]	1.473 (1.466–1.48)	1.304 (1.297–1.311)	1.65 (1.637–1.663)	1.363 (1.352–1.375)

[a]The variable network distance represents tens of kilometres (distance in km $\times 10^{-1}$) to facilitate interpretation of coefficients and enable model convergence.
[b]Seasonal trend was constructed as $[\sin(2\pi(\text{Month}_i + \theta/12]$, where θ was the horizontal shift that best fit the data of each model.
[c]Lagged trend transformed into visits per capita year to allow interpretation of results.

(Supplementary Table S2). After controlling for time trends and baseline differences in health system factors, patterns of geographic utilization of healthcare services were also highly sensitive to HSS programmes implemented in this period, especially the fee-exemption programme to increase financial access to PHC and the community program to address geographic barriers (Table 2). Both programmes had a positive impact on PHC utilization rates for all ages (OR = 1.09 and OR = 1.14, respectively), with a higher relative increase for those populations living further away (OR = 1.45 and OR = 1.09, respectively, every 10 km from a PHC). These results were consistent regardless of the age group considered or whether malaria cases were included in the model (Table 2). Our models accurately explained spatial and temporal utilization patterns at PHC (Supplementary Figure S4), allowing us to predict dynamics of PHC geographic utilization in the district (S2 Video).

Predictions from the model for all ages suggested that in the absence of these programmes, only 1% of the population in Ifanadiana district would have per capita PHC utilization of one visit or more per year and 12% would have 0.5 visits or more per year. If these programmes were implemented everywhere in the district, nearly one-quarter of the population (23%) would have a PHC utilization of at least one visit and nearly half (47%) would have at least 0.5 visits per capita year. Maps in Figure 4 show predictions of the geographic distribution of PHC utilization with and without implementation of HSS programmes, revealing substantial gaps in health system coverage for remote populations. PHC utilization remained low for remote populations under a variety of HSS scenarios that included hiring additional health staff at PHC, removing user fees and strengthening community health (Supplementary Figure S5).

Utilization for children under 5 years when combining PHC and community health consultations

To reduce geographic barriers to care, CHWs (two per fokontany) can manage childhood illnesses such as malaria, diarrhoea or pneumonia for children under 5 years of age. Data from community health sites in four communes of the HSS intervention area revealed that when combining outpatient visits from both PHC and community health sites for children under five, utilization of primary care in this period exceeded one visit per child for 39 of the 43 fokontany (94% of under-five population), regardless of the distance of the population to a PHC (Figure 5a). On average, combined utilization exceeded two visits per child per year in all distance groups from a PHC (Figure 5b). Average utilization at community health sites substantially increased at further distances from a PHC: annual utilization was less than 0.5 at 2.5 km from a PHC and nearly two at fokontany more than 15 km from a PHC. As a result, visits at community health sites accounted for 90% of total primary care visits in fokontany further than 15 km from a PHC, while they accounted for only 10% of total visits at 2.5 km or less from a PHC (Figure 5b). Combined utilization of primary care was still lower for children living further away from a PHC, but the effect of distance was much less

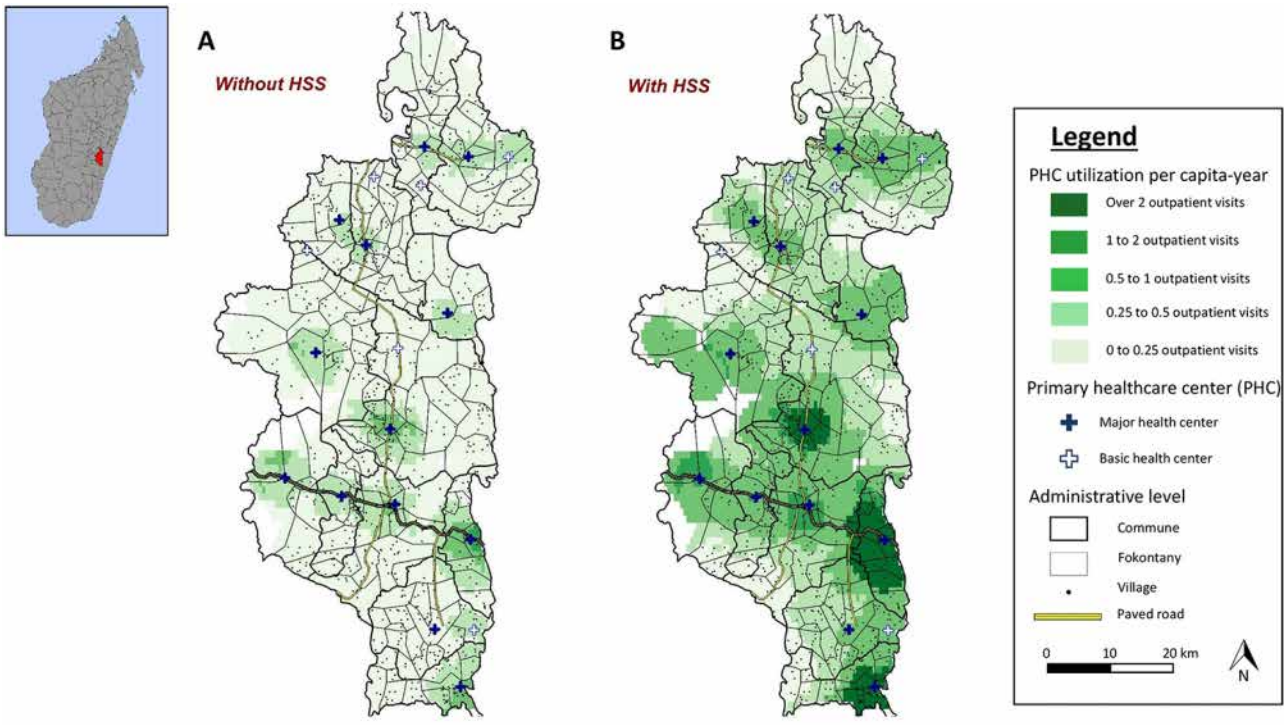

Figure 4. Predictions of geographic distribution of PHC per capita utilization in Ifanadiana district according to scenarios of HSS intervention implementation. Color shades represent predictions of annual PHC per capita visits in (A) a scenario where no HSS activities are implemented, and (B) a scenario where HSS are implemented in the whole district. Maps reveal that despite improvements, even if HSS were implemented across the district, a large proportion of the population would remain with very low levels of realized access to facility-based primary care.

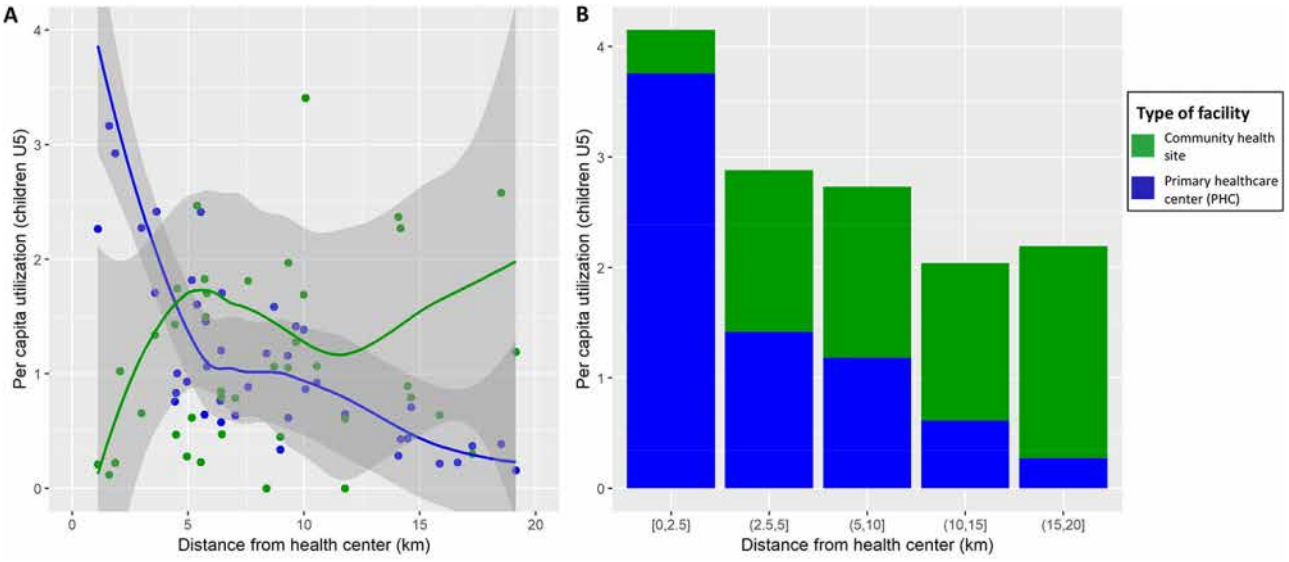

Figure 5. Annual utilization rates of primary care (PHC and community health sites) per capita by children under 5 years in the HSS intervention catchment, 2017. Graphs show per capita utilization at different distances to the nearest PHC, disaggregated by PHC and community health visits. It reveals that utilization at community health sites compensates the distance decay observed for PHC use, with higher community health site utilization at further distance to PHC and reaching over 2 visits per capita-year for all distance groups. To improve visualization, four dots were removed in the left graph (utilization over 4 per capita-year).

pronounced due to the exponential increase in community health site utilization at higher distances from PHC (Figure 5a), which essentially compensated for the distance decay.

Discussion

A renewed commitment to strengthening primary healthcare systems and ensuring UHC is essential to meet the health-related Sustainable Development Goals (United Nations

General Assembly, 2015), but enormous questions remain on how to do this (World Health Organization, 2018b; Stenberg *et al.*, 2017; Giedion *et al.*, 2013; Atun *et al.*, 2008; Hatt *et al.*, 2015). Here, we analysed geographic data from hundreds of thousands of patients in a rural district of Madagascar undergoing health system transformation to understand how facility- and community-based interventions contribute to health system coverage. Our results reveal that facility-based primary care has limited geographic coverage, even when it is free of charge at the point of service and of improved quality, the focus of most national UHC policies (Garchitorena *et al.*, 2017; Ezran *et al.*, 2019). Communities that lived within 5 km of a supported PHC exceeded one visit per person year, but the intervention accentuated the distance decay (exponential decrease) in PHC utilization and widened the gap with remote populations, which exacerbated disparities. We predict that scaling up PHC interventions alone (removing user fees and improving health system readiness) would only achieve modest increases in geographic coverage, with three-fourths of the population consulting at facilities less than once per person year. Strengthening community health can have substantial impacts on the geographic reach of the health system. The effect of geography on primary care access was greatly reduced for children under 5 years when considering community health consultations, reaching over two consultations per child year regardless of distance. CHWs were the main source of healthcare delivery for children in remote populations, representing 90% of primary care visits for those living further than 15 km from a PHC.

Research on geographic accessibility to care has generally focused on characterizing either potential access (population within a certain distance from a PHC) or realized access (actual utilization at different distances to a PHC) (Yao and Agadjanian, 2018; Chukwusa *et al.*, 2019). In terms of potential access, a travel time of 1 or 2 hours to health services is a typically accepted measure of accessibility to health services (Gething *et al.*, 2012; Pilcher *et al.*, 2014; Noor *et al.*, 2006; Juran *et al.*, 2018; Bailey *et al.*, 2011). We estimated distance to PHC using a complete district mapping of over 20 000 km of footpaths and 100 000 houses. We then parametrized travel time with hundreds of hours of fieldwork and remote sensing analyses. This approach allowed us to improve on previous methods in developing countries that use either Euclidean distances, friction surfaces (Stock, 2012; Makanga *et al.*, 2016; Munyaneza *et al.*, 2018) or self-reported answers in surveys (Gething *et al.*, 2012; Noor *et al.*, 2003; Al-Taiar *et al.*, 2010). We found that the majority of the population in Ifanadiana district (75%) lived more than 1 h from primary care at a PHC and over one-third (38%) lived further than 2 h. These figures are significantly worse than regional estimates of primary healthcare access in sub-Saharan Africa (Weiss *et al.*, 2020) and more comparable to estimated access to secondary care at hospitals in the region (Juran *et al.*, 2018; Ouma *et al.*, 2018). This may suggest that either access to care in Ifanadiana is indeed far worse than average or multi-country approaches tend to underestimate the proportion of the population with poor access to care, or both.

When user fees were removed and HSS activities were in place, we found that utilization rates reached between one and three consultations per person year for populations in close proximity to PHC, similar to findings in other studies in Africa (Zombré *et al.*, 2017), and close to utilization rates in many OCDE countries with lower disease burdens (Consultations with doctors, 2018). This suggests that UHC policies can be effective at increasing healthcare use to internationally acceptable levels for some populations. Yet, although distance to PHC is not always associated with lower utilization or worse outcomes (Munyaneza *et al.*, 2018; Lankowski *et al.*, 2014; Gething *et al.*, 2004), we observed a similar distance decay in utilization as previously described in other settings (Feikin *et al.*, 2009; McLaren *et al.*, 2014; Gething *et al.*, 2012; Noor *et al.*, 2003; Stock, 2012; Kelly *et al.*, 2016). Moreover, we show that this decay can be even more pronounced once interventions aimed at increasing healthcare access have been implemented. We found that the median distance of patients to PHC following the HSS was 2 km, similar to results found in a rural area of Western Kenya (Feikin *et al.*, 2009). Our results are also consistent with evidence from Burkina Faso and Ghana, where user-fee exemptions and HSS strategies achieved greater equity across socio-economic groups but did not overcome geographic barriers (Langlois *et al.*, 2016; De Allegri *et al.*, 2011; Mills *et al.*, 2008; De Allegri *et al.*, 2015; Hounton *et al.*, 2008). This puts into question the assumption that UHC policies alone, when they are in place and effective, can ensure the provision of primary healthcare services 'for everyone, everywhere'.

Using geographic information from nearly 300 000 primary care visits to PHC, we show that health system data can allow for powerful studies of spatio-temporal changes in healthcare access and for drawing key insights to improve UHC strategies. Previous studies that combined measures of geographic access with healthcare utilization or service coverage have been restricted to discrete services or conditions such as obstetric care, tuberculosis, malaria and HIV (Noor *et al.*, 2003; 2006; Munyaneza *et al.*, 2018; Lankowski *et al.*, 2014; Ebener *et al.*, 2015; Kuupiel *et al.*, 2019). Electronic health management information system (HMIS) data currently available rarely include a low level of geographic disaggregation, so studies typically use information from national surveys or restrict the extraction of HMIS geographic information to particular conditions (Langlois *et al.*, 2016; McLaren *et al.*, 2014; De Allegri *et al.*, 2011; 2015; Buor, 2003; Rosero-Bixby, 2004; Ruktanonchai *et al.*, 2016) or to small samples of patients (Stock, 2012; Gething *et al.*, 2004). One of the most precise studies linked over 3000 paediatric health visits in seven clinics in Kenya to individual identifiers from a demographic surveillance system (Feikin *et al.*, 2009). However, a push for electronic data collection to improve health information systems is underway in many developing countries, thanks to the scale up of the open source DHIS2 (District Health Information Software) among other platforms, which can be combined with community-based mobile tools for registering cases and track patient-level data at different levels of care (Dehnavieh *et al.*, 2018). The level of granularity and timeliness of data of these e-health platforms will open new possibilities for integration of feedback loops between spatial modelling approaches in local planning and implementation of health strategies to maximize geographic access.

Our study had several limitations. First, our estimates of travel time were based on speeds recorded in fieldwork done by health workers and community members, so they represent local travel time for healthy individuals. Other groups such as ill individuals, pregnant women or the elderly likely take longer to reach health facilities, and factors such as break time during a route that were not considered here could be particularly relevant for long distances. As a result, even our locally

calibrated results on travel time may be underestimating true travel time for certain vulnerable groups. Second, in this study we assessed aggregate changes in per capita utilization by fokontany and compared differences between catchment areas rather than evaluating individual patient itineraries. A study on prenatal care in Mozambique showed that although most women living near a PHF used the closest facilities, those who lived more than 5.5 km away could travel to a further PHF to seek better services (Yao and Agadjanian, 2018). If patients from outside the HSS catchment preferred to attend a HSS-supported PHC despite further distance, this could have resulted in an underestimation of the intervention effects. Third, studies in Ghana and Nigeria found that the distance decay was more important for illiterate, low-income, women, children and elderly populations (Stock, 2012; Buor, 2003), but we could only test for the decay in different age groups because it was the only demographic information collected. Finally, like for any local study, the generalizability of results presented here may be limited to other rural, low-income settings with similar characteristics as Ifanadiana in terms of geography, socio-economic level and health system factors. Further research is needed to assess whether similar effects of UHC and community health policies on primary care access are observed elsewhere.

In conclusion, the results from this study have important implications for the UHC strategy in Madagascar and other low-income countries, suggesting that wider support to community health may be necessary to achieve universal access to primary care. Although there remains debate on how to optimize community health, a greater ability for populations to reach facilities is critical in order to directly address the geographic burden of disease, and professionalized CHWs could contribute to this by expanding the scope of primary care services they provide across a greater range of clinical cases and demographic groups. More generally, we show how a model system in global health—based on the dynamic integration of data and services at multiple levels of the health system in geographically constrained areas—can help address fundamental questions on key global health policy issues.

Supplementary data

Supplementary data are available at *Health Policy and Planning* online.

Data availability statement

Data are available upon request to the address research@pivotworks.org.

Funding

This work was supported by a grant from Institut de Recherche pour le Developpement (Project IRD Coup de Pouce 'MAGIE') and internal funding from PIVOT.

Acknowledgements

We are grateful to everyone who contributed to the participatory mapping of Ifanadiana, especially Jérémy Commins, and Blake Girardot for setting the HOT projects online. We thank the staff of the local Ministry of Health team in Ifanadiana district as well as PIVOT's monitoring and community teams for their support during data collection. Thanks are due to Benjamin Andriamihaja and Tanjona Andréambeloson for their help at different stages of the project.

Ethical approval

Use of MoH data for this study was authorized by the Secretary General of the MoH, by the Medical Inspector of Ifanadiana district and by Harvard's Institutional Review board (IRB20-1247).

Author contributions

Conceived and designed the experiments: A.G., C.R., L.F.C., V.H. and M.H.B. Performed the analysis: A.G., F.A.I., C.R., M.R., V.H. and M.H.B. Contributed reagents/materials/analysis tools: A.G., C.R., V.H. and M.H.B. Wrote the paper: A.G., F.A.I., C.R., L.F.C., M.R., B.R., F.H.R., K.E.F., J.C.A., J.R., V.H. and M.H.B.

Conflict of interest statement

Some authors are current or former employees of institutions discussed in this article, including the NGO PIVOT and the Government of Madagascar. These affiliations are explicitly listed in the article.

References

Ahmed HM, Mitchell M, Hedt B. 2010. National implementation of Integrated Management of Childhood Illness (IMCI): policy constraints and strategies. *Health Policy* **96**: 128–33.

Al-Taiar A, Clark A, Longenecker JC, Whitty CJM. 2010. Physical accessibility and utilization of health services in Yemen. *International Journal of Health Geographics* **9**: 1–8.

Atun RA, Bennett S, Duran A. 2008. When do vertical (stand-alone) programmes have a place in health systems? *WHO European Ministerial Conference on Health Systems*: 1–28. https://apps.who.int/iris/handle/10665/107977.

Bailey PE, Keyes EB, Parker C *et al.* 2011. Using a GIS to model interventions to strengthen the emergency referral system for maternal and newborn health in Ethiopia. *International Journal of Gynecology & Obstetrics* **115**: 300–9.

Bates MA, Glennerster R, Gumede K, Duflo E The price is wrong. *Field Actions Science Reports* 2012. Special issue 4. http://factsreports.revues.org/1554.

Bonds MH, Garchitorena A, Cordier L *et al.* 2017. Advancing a science of sustaining health: a new platform for a model district in Madagascar. *bioRxiv*: 141549.

Buor D. 2003. Analysing the primacy of distance in the utilization of health services in the Ahafo-Ano South district, Ghana. *The International Journal of Health Planning and Management* **18**: 293–311.

Chukwusa E, Verne J, Polato G *et al.* 2019. Urban and rural differences in geographical accessibility to inpatient palliative and end-of-life (PEoLC) facilities and place of death: a national population-based study in England, UK. *International Journal of Health Geographics* **18**: 8.

Consultations with doctors. 2018. *Health at a Glance 2017: OECD Indicators*. Paris: OECD Publishing, 168–9.

Cordier LF, Kalaris K, Rakotonanahary RJL *et al.* 2020. Networks of care in rural Madagascar for achieving universal health coverage in Ifanadiana district. *Health Systems & Reform* **6**: 2–e1841437.

De Allegri M, Ridde V, Louis VR *et al.* 2011. Determinants of utilisation of maternal care services after the reduction of user fees: a case study from rural Burkina Faso. *Health Policy* **99**: 210–8.

De Allegri M, Tiendrebéogo J, Müller O *et al.* 2015. Understanding home delivery in a context of user fee reduction: a cross-sectional mixed methods study in rural Burkina Faso. *BMC Pregnancy Childbirth* **15**: 330.

Dehnavieh R, Haghdoost AA, Khosravi A *et al.* 2019. The District Health Information System (DHIS2): a literature review and meta-synthesis of its strengths and operational challenges based on the experiences of 11 countries. *Health Information Management Journal* **48**: 62–75.

Dhillon RS, Bonds MH, Fraden M, Ndahiro D, Ruxin J. 2011. The impact of reducing financial barriers on utilisation of a primary health care facility in Rwanda. *Global Public Health* **2007**: 1–16.

Ebener S, Guerra-Arias M, Campbell J *et al.* 2015. The geography of maternal and newborn health: the state of the art. *International Journal of Health Geographics* **14**: 19.

Ezran C, Bonds MH, Miller AC *et al.* 2019. Assessing trends in the content of maternal and child care following a health system strengthening initiative in rural Madagascar : a longitudinal cohort study. *PLoS Medicine* **16**: 1–23.

Feikin DR, Nguyen LM, Adazu K *et al.* 2009. The impact of distance of residence from a peripheral health facility on pediatric health utilisation in rural western Kenya. *Tropical Medicine & International Health* **14**: 54–61.

Fullman N, Barber RM, Abajobir AA *et al.* 2017. Measuring progress and projecting attainment on the basis of past trends of the health-related Sustainable Development Goals in 188 countries: an analysis from the Global Burden of Disease Study 2016. *Lancet* **390**: 1423–59.

Garchitorena A, Miller AC, Cordier LF *et al.* 2018. Early changes in intervention coverage and mortality rates following the implementation of an integrated health system intervention in Madagascar. *BMJ Global Health* **3**: e000762.

Garchitorena A, Miller AC, Cordier LF *et al.* 2017. In Madagascar, use of health care services increased when fees were removed: lessons for universal health coverage. *Health Affairs* **36**: 1443–51.

Gething PW, Johnson FA, Frempong-Ainguah F *et al.* 2012. Geographical access to care at birth in Ghana: a barrier to safe motherhood. *BMC Public Health* **12**: 1.

Gething PW, Noor AM, Zurovac D *et al.* 2004. Empirical modelling of government health service use by children with fevers in Kenya. *Acta Tropica* **91**: 227–37.

Giedion U, Alfonso EA, Díaz Y. 2013. *The Impact of Universal Coverage Schemes in the Developing World: A Review of the Existing Evidence*. Washington, DC: UNICO Studies Series.

Government of Madagascar. 2015. *Strategie Nationale sur la Couverture Sante Universelle, Madagascar*. Antananarivo: Government of Madagascar.

Hatt L, Johns B, Connor C *et al.* 2015. *Impact of Health Systems Strengthening on Health*. Bethesda, MD: Health Finance and Governance Project, Abt Associates Inc.

Hounton S, Chapman G, Menten J *et al.* 2008. Accessibility and utilisation of delivery care within a Skilled Care Initiative in rural Burkina Faso. *Tropical Medicine & International Health* **13**: 44–52.

Humanitarian OpenStreetMap Team. 2019. www.hotosm.org, accessed 1 December 2019.

Ihantamalala FA, Herbreteau V, Revillion C *et al.* 2020. Improving geographical accessibility modeling for operational use by local health actors. *Int J Health Geogr*. **19**: 27.

Institut National de la Statistique. 2009. *Enquête Démographique et de Santé, Madagascar*. Antananarivo: Institut National de la Statistique.

Johri M, Ridde V, Heinmüller R, Haddad S. 2014. Estimation of maternal and child mortality one year after user-fee elimination: an impact evaluation and modelling study in Burkina Faso. *Bulletin of the World Health Organization* **92**: 706–15.

Juran S, Broer PN, Klug SJ *et al.* 2018. Geospatial mapping of access to timely essential surgery in sub-Saharan Africa. *BMJ Global Health* **3**: e000875.

Kashima S, Suzuki E, Okayasu T *et al.* 2012. Association between proximity to a health center and early childhood mortality in madagascar. *PLoS One* **7**: e38370.

Kelly C, Hulme C, Farragher T, Clarke G. 2016. Are differences in travel time or distance to healthcare for adults in global north countries associated with an impact on health outcomes? A systematic review. *BMJ Open* **6**: 1–9.

Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. 2015. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ* **350**: h2750.

Kuupiel D, Adu KM, Apiribu F *et al.* 2019. Geographic accessibility to public health facilities providing tuberculosis testing services at point-of-care in the upper east region, Ghana. *BMC Public Health* **19**: 1–12.

Lagarde M, Palmer N. 2011. The impact of user fees on access to health services in low- and middle-income countries. *Cochrane Database of Systematic Reviews*.

Langlois ÉV, Karp I, De Dieu Serme J, Bicaba A. 2016. Effect of a policy to reduce user fees on the rate of skilled birth attendance across socioeconomic strata in Burkina Faso. *Health Policy and Planning* **31**: 462–71.

Lankowski AJ, Siedner MJ, Bangsberg DR, Tsai AC. 2014. Impact of geographic and transportation-related barriers on HIV outcomes in sub-saharan Africa: a systematic review. *AIDS and Behavior* **18**: 1199–223.

Makanga PT, Schuurman N, Von Dadelszen P, Firoz T. 2016. A scoping review of geographic information systems in maternal health. *Int J Gynecol Obstet. International Federation of Gynecology and Obstetrics* **134**: 13–7.

McLaren Z, Ardington C, Leibbrandt M. 2014. Distance decay and persistent health care inequality in South Africa. *BioMed Cent* **14**: 541.

Mills S, Williams JE, Adjuik M, Hodgson A. 2008. Use of health professionals for delivery following the availability of free obstetric care in Northern Ghana. *Maternal and Child Health Journal* **12**: 509–18.

Munyaneza F, Ntaganira J, Nyirazinyoye L *et al.* 2018. Community-based accompaniment and the impact of distance for HIV patients newly initiated on antiretroviral therapy: early outcomes and clinic visit adherence in rural Rwanda. *AIDS and Behavior* **22**: 77–85.

Nguyen HT, Zombré D, Ridde V, De Allegri M. 2018. The impact of reducing and eliminating user fees on facility-based delivery: a controlled interrupted time series in Burkina Faso. *Health Policy and Planning* **33**: 948–56.

Noor AM, Amin AA, Gething PW *et al.* 2006. Modelling distances travelled to government health services in Kenya. *Tropical Medicine and International Health* **11**: 188–96.

Noor AM, Zurovac D, Hay SI, Ochola SA, Snow RW. 2003. Defining equity in physical access to clinical services using geographical information systems as part of malaria planning and monitoring in Kenya. *Tropical Medicine and International Health* **8**: 917–26.

Ouma PO, Maina J, Thuranira PN *et al.* 2018. Access to emergency hospital care provided by the public sector in sub-Saharan Africa in 2015: a geocoded inventory and spatial analysis. *The Lancet Global Health* **6**: e342–50.

Pilcher J, Kruske S, Barclay L. 2014. A review of rural and remote health service indexes: are they relevant for the development of an Australian rural birth index? *BMC Health Services Research* **14**: 1–8.

R Development Core Team. 2011. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing.

Rosero-Bixby L. 2004. Spatial access to health care in Costa Rica and its equity: a GIS-based study. *Social Science & Medicine* **58**: 1271–84.

Ruktanonchai CW, Ruktanonchai NW, Nove A *et al.* 2016. Equality in maternal and newborn health: modelling geographic disparities

in utilisation of care in five East African countries. *PLoS One* **11**: 1–17.

Sachs JD. 2012. Achieving universal health coverage in low-income settings. *The Lancet* **380**: 944–7.

Stenberg K, Hanssen O, Edejer TTT *et al.* 2017. Financing transformative health systems towards achievement of the health Sustainable Development Goals: a model for projected resource needs in 67 low-income and middle-income countries. *The Lancet Global Health* **5**: e875–87.

Stock R. 2012. Distance and utilization of health facilities in rural Nigeria. *Social Science & Medicine* **17**: 563–70.

United Nations General Assembly. 2015. *Transforming Our World: The 2030 Agenda for Sustainable Development*, New York, USA: United Nations.

Weiss DJ, Nelson A, Vargas-Ruiz CA *et al.* 2020. Global maps of travel time to healthcare facilities. *Nature Medicine* **26**: 1835–1838.

The World Bank. 2012. *Emergency Support to Critical Education, Health and Nutrition Services Project*, Washington DC: The World Bank.

The World Bank. World Health Organization and the International Bank for Reconstruction and Development. Tracking Universal Health Coverage: 2017 Global Monitoring Report. 2017. ISBN 978-92-4-151355-5.

World Bank. 2019. *World Bank Open Data*. http://data.worldbank.org, accessed 20 December 2019.

World Health Organization. 2010. *Monitoring the Building Blocks of Health Systems: A Handbook of Indicators and Their Measurement Strategies*, 1–92. Geneva, Switzerland: World Health Organization.

World Health Organization. 2018a. *Declaration of Astana*. Geneva.

World Health Organization. 2018b. *WHO Guideline on Health Policy and System Support to Optimize Community Health Worker Programmes*. Geneva: World Health Organization.

World Health Organization. 2019. *Global Health Observatory Data Repository*. http://apps.who.int/gho/data/view.main.95000, accessed 22 December 2019.

WorldPop. 2017. *Madagascar 100m Population, Version 2*. University of Southampton, Southampton, England.

Yao J, Agadjanian V. 2018. Bypassing health facilities in rural Mozambique: spatial, institutional, and individual determinants. *BMC Health Services Research* **18**: 1–11.

Zombré D, De Allegri M, Ridde V. 2017. Immediate and sustained effects of user fee exemption on healthcare utilization among children under five in Burkina Faso: a controlled interrupted time-series analysis. *Social Science & Medicine* **179**: 27–35.

BMJ Global Health

Impact of health system strengthening on delivery strategies to improve child immunisation coverage and inequalities in rural Madagascar

Elinambinina Rajaonarifara,[1,2,3] Matthew H Bonds,[3,4] Ann C Miller,[4] Felana Angella Ihantamalala,[3] Laura Cordier,[3] Benedicte Razafinjato,[3] Feno H Rafenoarimalala,[3] Karen E Finnegan,[3,4] Rado J L Rakotonanahary,[3] Giovanna Cowley,[3] Baolova Ratsimbazafy,[3] Florent Razafimamonjy,[3] Marius Randriamanambintsoa,[5] Estelle M Raza-Fanomezanjanahary,[6] Andriamihaja Randrianambinina,[6] C Jessica Metcalf ,[7] Benjamin Roche,[2,8] Andres Garchitorena [2,3]

To cite: Rajaonarifara E, Bonds MH, Miller AC, *et al*. Impact of health system strengthening on delivery strategies to improve child immunisation coverage and inequalities in rural Madagascar. *BMJ Global Health* 2022;**7**:e006824. doi:10.1136/bmjgh-2021-006824

Handling editor Seye Abimbola

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgh-2021-006824).

Received 6 July 2021
Accepted 19 December 2021

For numbered affiliations see end of article.

Correspondence to
Elinambinina Rajaonarifara; elinambinina@gmail.com

ABSTRACT

Background To reach global immunisation goals, national programmes need to balance routine immunisation at health facilities with vaccination campaigns and other outreach activities (eg, vaccination weeks), which boost coverage at particular times and help reduce geographical inequalities. However, where routine immunisation is weak, an over-reliance on vaccination campaigns may lead to heterogeneous coverage. Here, we assessed the impact of a health system strengthening (HSS) intervention on the relative contribution of routine immunisation and outreach activities to reach immunisation goals in rural Madagascar.

Methods We obtained data from health centres in Ifanadiana district on the monthly number of recommended vaccines (BCG, measles, diphtheria, tetanus and pertussis (DTP) and polio) delivered to children, during 2014–2018. We also analysed data from a district-representative cohort carried out every 2 years in over 1500 households in 2014–2018. We compared changes inside and outside the HSS catchment in the delivery of recommended vaccines, population-level vaccination coverage, geographical and economic inequalities in coverage, and timeliness of vaccination. The impact of HSS was quantified via mixed-effects logistic regressions.

Results The HSS intervention was associated with a significant increase in immunisation rates (OR between 1.22 for measles and 1.49 for DTP), which diminished over time. Outreach activities were associated with a doubling in immunisation rates, but their effect was smaller in the HSS catchment. Analysis of cohort data revealed that HSS was associated with higher vaccination coverage (OR between 1.18 per year of HSS for measles and 1.43 for BCG), a reduction in economic inequality, and a higher proportion of timely vaccinations. Yet, the lower contribution of outreach activities in the HSS catchment was associated with persistent inequalities in geographical coverage, which prevented achieving international coverage targets.

Key questions

What is already known?

- Reaching the minimum recommended vaccination coverage of 90% for childhood illnesses remains a substantial challenge for low-income and middle-income countries (LMICs).
- Understanding how vaccine delivery strategies can be improved to achieve coverage targets in rural areas of LMICs is essential due to the fragility of health systems and associated health budgets.
- While evidence exists on the impact of outreach activities and other targeted interventions aimed at improving immunisation coverage, it is unclear how strengthening local health systems can help improve key indicators of vaccination coverage, via its different impacts on routine and outreach immunisations.

What are the new findings?

- A health systems strengthening (HSS) intervention in a rural district of Madagascar improved overall vaccination coverage, reduced economic inequalities in vaccination coverage and increased the proportion of timely vaccinations via an increase in routine immunisations.
- The contribution of outreach activities was lower in the HSS catchment area than in the rest of the district, which was associated with a persistence of geographical inequalities in vaccination coverage.

What do the new findings imply?

- Strengthening local health systems can help improve key indicators of vaccination coverage in rural, low resource settings, even when those interventions do not target specifically vaccine improvements themselves.
- Explicit efforts are still necessary in areas undergoing HSS to vaccinate children in remote areas so that immunisation goals can be reached.

Conclusion Investment in stronger primary care systems can improve vaccination coverage, reduce inequalities and improve the timeliness of vaccination via increases in routine immunisations.

INTRODUCTION

Vaccination is one of the most effective public health interventions to reduce the burden of infectious diseases, particularly among children.[1 2] To increase vaccination coverage around the world, the Global Alliance for Vaccines and Immunisation (GAVI) was created in 2000 to mobilise funds and technical expertise for child vaccination in the poorest countries in the world.[3 4] As a result, from 2000 to 2015, global vaccination coverage has increased from 72% to 86%.[5] As of 2018, 760 million children have been immunised and an estimated 13 million deaths have been prevented in GAVI-supported countries.[6] Future impacts of immunisations are estimated to be larger with the introduction of new vaccines (eg, rotavirus, papillomavirus) and the expansion of coverage for existing vaccines.[7 8] Based on the Global Immunisation Vision and Strategy, the goal of the Global Vaccine Action Plan was to reach a national coverage of 90% for basic vaccines in all countries in 2020,[8 9] with at least 80% coverage in every district.[10] Despite great progress, vaccination coverage remains low in many areas of the developing world due to many reasons.[11] For instance, while average coverage for third dose of the diphtheria, tetanus and pertussis (DTP) vaccine increased from 60% to 81% between 1999 and 2018 in low-income and middle-income countries (LMICs), it remained under 40% for the bottom ten performing countries.[5] Failure to achieve critical population-level thresholds for herd immunity has resulted in sustained transmission, periodic epidemics and has slowed-down progress towards the elimination of vaccine preventable diseases such as polio, measles and rubella.[12–14] Beyond 2020, the new objective of the GAVI strategy is to reduce the number of 'zero-dose' children by 25% in 2025 and by 50% in 2030.[15]

National strategies for vaccination in most LMICs typically involve routine immunisation (RI) at primary health centres, complemented with additional outreach activities to increase coverage such as periodic vaccination weeks (VW) and supplementary immunisation activities (SIAs) such as mass vaccination campaigns. RI, where a child is brought to a health facility to receive the recommended shots, usually free of charge, represents the most reliable way of vaccinating children at the right time in order to maximise immunity.[16] However, its reach is undermined by the fragility of health systems in LMICs and multiple barriers faced by local populations for accessing healthcare.[17] In particular, geographical distance to primary health centres is associated with important inequalities in vaccination coverage.[18] Vaccination campaigns, which involve the mobilisation of health workers to administer vaccines where populations live during VW and SIAs, are a very effective way to cover large geographical areas over short periods of time and to reduce geographical inequalities in vaccination coverage.[19 20] Consequently, significant funding has been mobilised towards increasing coverage via vaccination campaigns,[20 21] but the low frequency of these campaigns can result in heterogeneous coverage across age groups,[18 22] insufficient number of recommended doses per vaccine[23] and important delays in immunisation relative to the recommended age of vaccination.[24–27] In addition, vaccination campaigns can have negative impacts on subsequent rates of immunisation via RI,[13 28] which could exacerbate these issues. To address this, investments in vaccination campaigns could be accompanied with broader health system strengthening (HSS) efforts to increase the contribution of RI to overall immunisation coverage.[28 29]

Madagascar is illustrative of the challenges and potential solutions to achieving global goals for immunisation in LMICs. Since its launch in 1976, the national Expanded Programme on Immunisation (EPI) has contributed to a substantial uptake in immunisation[30 31] which seems to have been an important driver in improvements in life expectancy.[32] In addition to supporting RI activities, the EPI launched biannual VWs in 2006 ('mother and child weeks', which generally take place in April and November),[33–35] and conducts occasional SIAs to further increase coverage and prevent disease outbreaks.[13 36] As of 2018, vaccination coverage goals for Madagascar had not yet been achieved for any of the recommended vaccines.[37] Suboptimal vaccination coverage can lead to larger-than-usual outbreaks (known in epidemiology as 'posthoneymoon' epidemics)[13] . For instance, insufficient coverage for measles vaccine (~80% by 2017)[38] led to the largest known measles outbreak in Madagascar history in 2018–2019,[39] which accounted for one fourth of global cases[40] that year with nearly 225 000 cases registered.[41] Achieving vaccination coverage targets is particularly challenging in rural areas of the country, where the majority of the population lives, and where coverage is over 10% lower than in urban areas[37] for all recommended vaccines.

In 2014, the Ministry of Public Health (MoPH) partnered with the nongovernmental healthcare organisation PIVOT to strengthen the rural health district of Ifanadiana, located in southeastern Madagascar, to improve local health conditions and serve as a model health system for the country.[42] Though the partnership does not include a particular focus on immunisation (which is managed directly by the MoPH), it supports a large range of interventions at health centres and community health sites in approximately one-third of the district, which has resulted in substantial increases in primary healthcare access and utilisation.[43] Those programmes include improved 'readiness' of health facilities (staffing, training, equipment, infrastructure, supply chain) and clinical programmes that can directly influence adherence to vaccinations schedules, such as family planning, antenatal care, postnatal care and deliveries at health facilities.

The goal of this study was to assess the impact of HSS on the relative contribution of RI and vaccination campaigns over time, and the impact of these changes on key features of immunisation at the population-level. In particular, we assessed changes between 2014 and 2018 in the HSS catchment and in the rest of the district in (1) the delivery of recommended vaccines, (2) population-level vaccination coverage, (3) geographical and economic inequalities in coverage and (4) timeliness of vaccination. For this, we combined immunisation data from all health centres in Ifanadiana district with information from a district-representative longitudinal cohort conducted every 2 years in nearly 1600 households in the district (~8000 individuals).

METHODS

Study site

Ifanadiana is a rural district in the region of Vatovavy Fitovinany, located in southeastern Madagascar. It comprises about 200 000 people distributed in 13 communes, with 2 additional communes created during the study period. The district's health system consists of one hospital (CHRD) and at least one health centre (CSB2) per commune that provides primary healthcare. Six communes have additional health centres (CSB1) with more limited health services. The initial HSS catchment comprised 4 out of the 13 communes in the first 3 years (2014–2016). One additional commune was added in 2017 to the HSS catchment, with plans to progressively cover the entire district over the following years.[44] The HSS intervention spans across all levels of care (hospital, health centres and community health) and combines horizontal support to health system readiness (eg, infrastructure, staffing, equipment, removal of user fees, social support to patients) with vertical support to clinical programmes (eg, malnutrition, emergency care, tuberculosis) and improved information systems.[44 45] More details are available in online supplemental table S1.[46] Delivery of child immunisation is similar to the rest of Madagascar, combining RI with biannual VWs and other outreach activities. Only one SIA took place during the study period in Ifanadiana, a measles mass vaccination campaign in October 2016.

Data collection

Health system data collection

Data on monthly immunisation rates from 2014 to 2018 were obtained from all 19 primary health centres in Ifanadiana district. Two health centres that were recently built and lacked consistent data across the study period were excluded. Data were obtained on all recommended vaccines in the Madagascar EPI, which included tuberculosis (BCG), measles, polio and the combined vaccine for DTP. For polio and DTP, only the number of third doses administered was considered, which indicates completion of all the required doses for these two vaccines. Immunisation information was derived from the health centres' monthly reports to the district, which are aggregated from the health centres' registers every month by MoPH staff. From these, the number of children immunised per month for each of these vaccines was obtained for each health centre (CSB1 or CSB2), which included all children vaccinated through both routine services and outreach activities. The population of children aged 12–23 months was also obtained for each health centre catchment from official MoPH records.[47] Data quality were monitored by joint PIVOT-MoPH supervisions every 3 months. During each supervision, data from the health centre paper registries, containing each individual visit, were used to calculate a number of indicators (though the number of immunisations was not among them); values for each indicator were then compared with those reported in the monthly report to the district.[48] Information on the geographical extent and timing of the HSS intervention was obtained from the NGO's internal records.

Cohort data collection

We obtained population-level information from the Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation (IHOPE), a district-representative longitudinal cohort study initiated in Ifanadiana district in 2014.[49] It consists of a series of surveys conducted in a sample of 1600 households every 2 years, with questionnaires modelled after the internationally validated Demographic and Health Surveys (DHS).[50] A two-stage sample stratified the district by the initial HSS and control catchments. Eighty clusters, half from each stratum, were selected at random from enumeration areas mapped during the 2009 census, and households were then mapped within each cluster. Twenty households were selected at random from each cluster. A total of 1522 households were successfully interviewed in 2014 (95.1% acceptance rate), 1514 and 1512 households were revisited during the follow-up in 2016 (94.6% acceptance rate) and in 2018 (94.5% acceptance rate), respectively. Data collection, survey coordination and training were conducted by the Madagascar National Institute of Statistics.

The survey included a household questionnaire and individual questionnaires for all men and women of reproductive age (15–59 years and 15–49 years, respectively). All eligible women and men who were in the households sampled (usual residents or visitors) were interviewed. Data collected through the questionnaires included general information about household composition (size, genders, ages); living conditions, education, and other indicators of socioeconomic status; recent illness, care seeking for illness and preventive behaviours; women's reproductive history and care seeking behaviour for reproductive health; children's health, development, preventive behaviours and care seeking for illness; and child, adult and maternal mortality. For vaccination specifically, information about vaccination status of the children under 5 years was obtained from the individual interviews with their mothers. Vaccination

status and history was assessed from the children's vaccination cards when available, or from the mother's report otherwise.

Use of aggregated HMIS data was authorised by the Ministry of Public Health's Medical Inspector in Ifanadiana district.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Data analysis

Analysis of immunisation rates at health centres

We studied the effect of the VWs and the HSS intervention on monthly immunisation rates at health centres over the study period. For this, we first estimated monthly per capita rates (age-specific) at each health centre for each vaccine (BCG, polio third dose, DTP third dose and measles). Per capita immunisation rates were modelled separately for each vaccine via binomial regressions in generalised linear mixed models, including a random intercept for each health centre. All explanatory variables (see below) were included as fixed effects. To study the effect of VWs and of the HSS intervention on immunisation rates, we built dummy variables coded as 1 for the CSBs and months where each programme was in place (discrete for months with VWs, and constant from the moment the HSS started until the end of the study period). We also studied the interaction of the HSS intervention with a linear annual change and VWs, in order to account for the additional effect of the HSS intervention over time, and for changes in the contribution of VWs to overall immunisation rates due to the HSS intervention, respectively. We controlled our analyses for baseline differences in health system factors and time-varying factors, which is akin to a difference-in-differences analysis. For health system factors, we controlled for baseline differences between health centres in the initial HSS catchment and in the rest of the district, as well as between different types of health centre (CSB1 and CSB2). For time-varying factors, we controlled for annual linear and seasonal changes in immunisation rates in the district. Seasonal changes were studied using a sine function with a period of 1 year and the horizontal shift that best fitted the data. We excluded from the analysis the measles immunisations delivered via SIAs in October 2016 because the target age was children up to 5 years of age, which differed from the population group used in the analyses (12–23 months).

Univariate analyses were first performed for each explanatory variable and those with $p<0.1$ were retained for multivariate analysis. From this full model, a reduced model that included only variables reaching statistical significance ($p<0.05$) was obtained via backwards selection. Effects are reported as adjusted ORs.

Analysis of vaccination coverage in the longitudinal cohort

While an analysis of health centre immunisations can provide some basic understanding about the impact of the HSS intervention on RI and outreach activities over time, it does not allow for obtaining accurate measures of vaccination coverage due to known inaccuracies in target population estimates, which are often based on extrapolation of data from censuses conducted very far apart in time.[51–53] In addition, aggregated information reported by the health system does not allow us to evaluate changes in economic or geographical inequalities in vaccination coverage, or for the assessment of the timeliness of vaccination, all of which can be affected by the relative contribution of RI and outreach activities in the area. For this, we conducted a complementary analysis of vaccination coverage at the population-level using data from the IHOPE cohort.

Vaccination coverage was estimated for 2014, 2016 and 2018 from individual level data for children 12–23 months or 12–59 months (depending on the analysis, see below), as the proportion of the target group immunised at the time of the interview. Similar to our analysis of health centre immunisation rates, we studied separately each of the recommended vaccines, namely BCG, polio third dose, DTP third dose and measles. We also estimated whether the child had received all of these recommended vaccines. For each child surveyed, vaccination status for each vaccine was coded 1 if the child was vaccinated based either on the vaccination cards, or on the mother's report, and 0 otherwise. To assess the impact of economic and geographical inequalities in vaccination coverage, we estimated a household wealth score via principal components analysis of household assets following standard DHS methods,[50] and we estimated the shortest path distance from the villages in each cohort cluster to the nearest health centre using the Open Source Routing Machine engine. For this, we had previously mapped the entire district of Ifanadiana on OpenStreetMap, resulting in over 23 000 km of footpaths and 5000 residential areas mapped.[54] Households were ordered based on their wealth score and distance to the nearest health centre and were classified into five quantiles with 20% of observations in each category (Q5=wealthiest or closest to the health centre; Q1=poorest or most remote). Vaccination coverage in children 12–23 months was estimated inside and outside of the HSS catchment at the beginning and at the end of the study period (2014–2018), disaggregated by wealth quantile and by distance quantile. Consistent with previous studies, changes in inequalities were measured as the gap in vaccination coverage between the worst-off quantiles (Q1–Q2) and the best-off quantiles (Q3–Q5) over time.[43 55 56]

We then modelled changes in vaccination coverage over the study period, studying baseline differences and annual changes in overall coverage and in economic and geographical inequalities for the HSS catchment and the rest of the district. For this, we performed a separate logistic regression mixed model for each vaccine, with

the household cluster as random intercept. To study baseline differences between HSS catchments we included a dummy variable reflecting whether clusters where located in the initial HSS catchment. We included the natural logarithm of the wealth score to study differences in socioeconomic groups, and distance to health centre (in tens of kilometres) to study differences in geographical groups, both as continuous variables. We included two time-varying variables, one to reflect annual changes in vaccination coverage in the whole district, and another to reflect changes per year of HSS intervention in the HSS catchment. Finally, we included interaction terms of these two variables with wealth and distance to study the evolution of inequalities in each area. We included children aged 12–59 months in these analyses to allow for adequate sample sizes for each model. Model selection procedures were identical to those described above for the analysis of health system data. To understand which population groups could reach recommended vaccination coverage targets in the HSS catchment and in the rest of the district, we predicted in-sample vaccination coverage for 2018 from each of the reduced multivariate models, at varying levels of socioeconomic class and proximity to health centres.

Finally, we studied the difference in timeliness of vaccination between the HSS catchment and the rest of the district in the subset of children 12–59 months with vaccination cards at the time of the interview in any of the cohort waves (N=786). For this, we estimated the child's age at vaccination from the date of birth and the date of vaccination. Timely vaccination was estimated for each vaccine based on the recommended age of vaccination by the national EPI in Madagascar: in the first month of life for BCG (recommended to be given at birth), in the fourth month for polio third dose and DTP third dose (recommended to be given the 14th week), and in the 9th month for measles.[37]

RESULTS

Trends in the rates of per capita immunisation at Ifanadiana's health centres

Between January 2014 and December 2018, a total of 28 407 BCG, 31 476 polio third dose, 33 241 DTP third dose and 30 371 measles immunisations were delivered by the 19 health centres in Ifanadiana District. Average monthly per capita immunisation rates (age specific, children 12–23 months) at health centres varied from 0.02 to 0.21, with an average of 0.08. Higher rates were observed on average in the HSS catchment, during months where VWs took place and with an apparent increase over time in the whole district (figure 1). These immunisation trends were similar for all the different vaccines considered (figure 1). Results from multivariate analyses revealed that per capita immunisation rates were similar for different types of health centre and HSS catchment at baseline (table 1). Immunisation rates for all vaccines increased over time and varied seasonally, with higher rates during the dry season (peak in August) and lower rates during the rainy season (bottom in February). Annual increase was higher for BCG and measles (OR 1.23 and 1.1, respectively), which require one single dose, than for polio and DTP (OR=1.06 for both), which require three doses. VWs were associated with approximately a doubling in immunisation rates in the months where they took place (OR between 1.88 measles and 2 for polio).

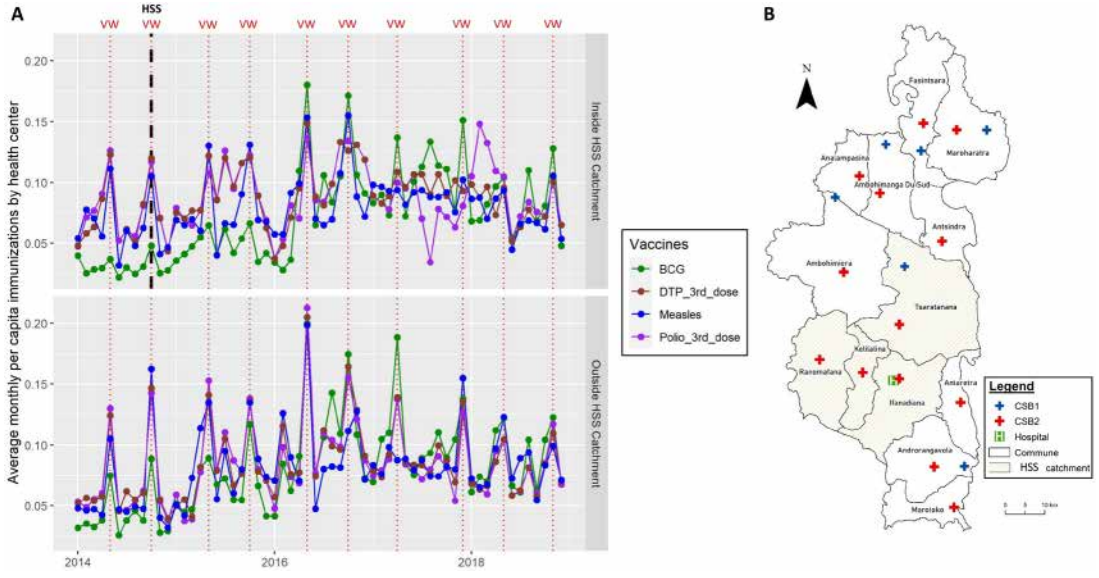

Figure 1 Changes in monthly immunisation rates for children 12–23 months at health facilities in Ifanadiana District, 2014–2018. (A) Average number of monthly immunisations per capita (age-specific, 12–23 months) delivered by health centres over time in the HSS catchment and in the rest of the district, with colours representing different vaccines. (B) Map of Ifanadiana district and its health facilities. The initial HSS catchment is shown as yellow shaded areas, whereas the rest of the district is shown as white areas. DTP, diphtheria, tetanus and pertussis; HSS, health system strengthening; VW, vaccination weeks.

Table 1 Determinants of per capita monthly immunisations at health centres in Ifanadiana district, 2014–2018 (Generalized Linear Mixed Model (GLMM), multivariate results*)

Variable	BCG immunisations	Polio immunisation (third dose)	DTP immunisation (third dose)	Measles immunisation
Monthly coverage at baseline (intercept)	0.04 (0.03 to 0.04)	0.06 (0.06 to 0.07)	0.06 (0.06 to 0.07)	0.06 (0.05 to 0.06)
Time-varying factors				
Annual change	1.23 (1.22 to 1.25)	1.06 (1.05 to 1.07)	1.06 (1.05 to 1.07)	1.1 (1.09 to 1.11)
Seasonal changes	1.05 (1.03 to 1.07)	1.05 (1.03 to 1.07)	1.06 (1.04 to 1.08)	0.98 (0.96 to 1)
Effect of programmes and policies				
Mother and child week (2 months per year)	1.95 (1.89 to 2.02)	2 (1.93 to 2.06)	1.95 (1.89 to 2.01)	1.88 (1.82 to 1.95)
Health system strengthening (HSS)	1.4 (1.29 to 1.52)	1.34 (1.25 to 1.44)	1.49 (1.39 to 1.6)	1.22 (1.14 to 1.32)
HSS×annual change	0.95 (0.93 to 0.97)	0.92 (0.91 to 0.94)	0.91 (0.9 to 0.93)	0.92 (0.91 to 0.94)
HSS×mother and child weeks	0.73 (0.69 to 0.77)	0.62 (0.58 to 0.66)	0.65 (0.61 to 0.69)	0.77 (0.73 to 0.82)

*Results are expressed as probabilities for the intercept and as OR with associated 95% CIs for all other variables. Models initially controlled for health system factors (type of health centre and baseline differences in HSS catchment vs control) but these were removed in the final reduced models for lack of statistical association.
DTP, diphtheria, tetanus and pertussis.

The HSS intervention, implemented since October 2014 in one-third of Ifanadiana district, was associated with a significant increase in immunisation rates (OR between 1.22 for measles and 1.49 for DTP), although this effect diminished over time (OR for interaction of HSS with annual change between 0.91 for DTP and 0.95 for BCG). Interestingly, the relative contribution of VWs to overall immunisation rates was lower in the HSS catchment following the HSS intervention, with an OR for the interaction with VWs between 0.62 for polio and 0.77 for measles (table 1). Full multivariate models that included all explanatory variables regardless of statistical significance (online supplemental table S4) had results consistent with those described here using reduced models, although estimates of HSS impact were smaller in considering the full set of control variables.

Changes in population-level vaccination coverage from the longitudinal cohort

Trends in vaccination coverage and inequalities

In total, data from 2699 children between 12 and 59 months of age were obtained from the longitudinal cohort. Of these, 651 were between 12 and 23 months old, the age at which all four immunisations studied here should be completed. Vaccination coverage for children 12–23 months was very low at baseline, ranging from about 54%–59% depending on the vaccine. Only 34.6% of children 12–23 months were fully vaccinated in 2014. Consistent with analyses of health system data, coverage for most vaccines improved substantially during the study period, especially in the HSS catchment (figure 2). In 2018, 63.6% were fully vaccinated in the HSS area, compared with only 37.5% in the rest of the district. Coverage in 2018 varied for each vaccine considered; BCG had the highest coverage (80.8% inside and 70.3% outside the HSS catchment), whereas measles had the lowest coverage (73.2% inside and 49.2% outside the HSS catchment). The minimum recommended coverage of 90% was not reached for any of the vaccines, either inside or outside the HSS catchment.

Disparities in immunisation coverage were observed according to households' geographical distance to health centres and wealth, with different trends in the HSS catchment and in the rest of the district (figure 2). In 2014, the difference in coverage between households living closer (quantiles Q3–Q5) and further (Q1–Q2) from health centres ranged from 25% to 32%, except for measles vaccine. Differences between wealthier (Q3–Q5) and poorer (Q1–Q2) households were smaller, between 5% and 15% for most vaccines. After 4 years, economic inequalities in vaccination coverage were substantially reduced in the HSS catchment, with little change in geographical inequalities. In contrast, in the rest of the district geographical inequalities were greatly reduced, while economic inequalities increased for all vaccines except for polio. Online supplemental table S2 shows vaccination coverage rates in each of the cohort years (2014, 2016 and 2018) and these different population groups.

Determinants of vaccination coverage trends and predictions of coverage targets

Multivariate analyses of vaccination coverage trends between 2014 and 2018 revealed consistent predictors for most of the vaccines studied (table 2). Baseline differences between the HSS catchment and the rest of the district were observed for only two vaccines, BCG (OR=0.6) and DTP (OR=1.65). Coverage of each of the four vaccines was positively associated with household wealth and negatively associated with household distance to health centres. The odds of vaccination for children in remote households was between half (OR=0.52, measles) and a fifth (OR=0.22, BCG) for every additional 10 km from the nearest health centre. Vaccines with three

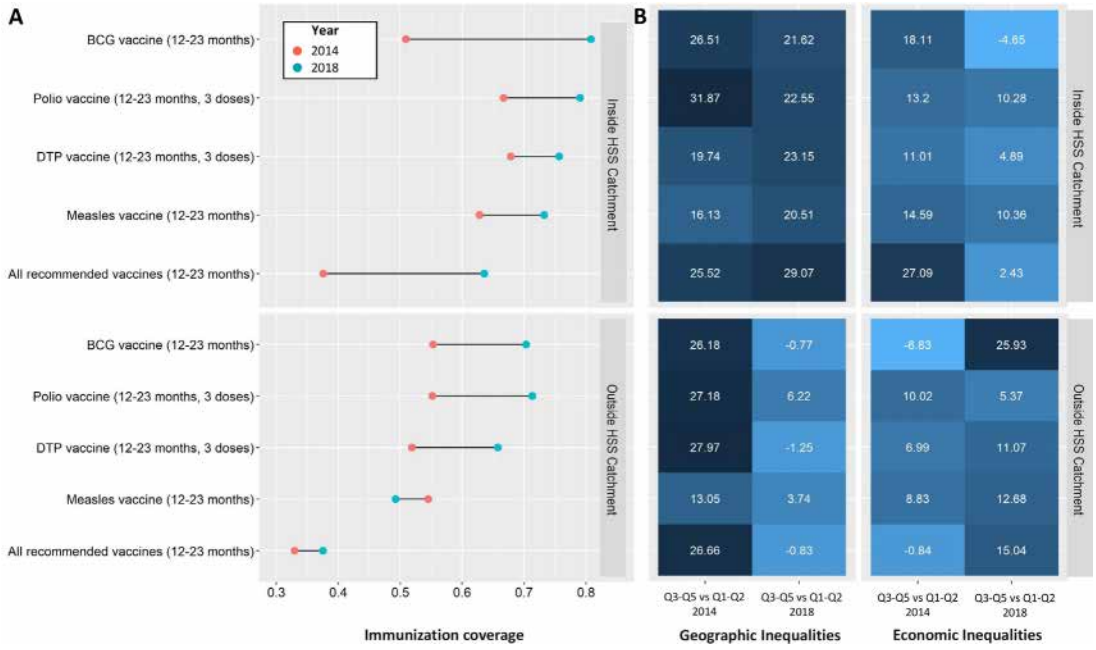

Figure 2 Changes in vaccination coverage for children 12–23 months and associated inequalities in Ifanadiana district, 2014–2018. (A) shows changes in immunisation coverage over time, split by HSS catchment and type of vaccine. (B) shows inequalities in coverage over time, according to geographical quantiles (distance to health centre, left panel) and economic quantiles (wealth score, right panel). Colour gradient shows the difference in coverage between the best-off groups (quantiles 3–5) and the worst-off groups (quantiles 1 and 2), from dark blue (greater difference, more inequalities) to light blue (smaller difference, less inequalities). Results from an equivalent analysis of inequalities but comparing Q4–Q5 vs Q1–Q2 is available in online supplemental figure S2. DTP, diphtheria, tetanus and pertussis; HSS, health system strengthening.

required doses were the most associated with household wealth, with an OR of 2.58 for DTP and 2.85 for polio. District-wide improvements in vaccination coverage were associated with a reduction in geographical inequalities over time and not with a homogeneous improvement for all population groups. Indeed, the OR of the interaction between annual change and distance to health centre ranged from 1.17 (all vaccines) and 1.31 (BCG and polio), meaning that each year households living far from health centres had progressively better coverage, closing the gap with those living in close proximity. Changes in the HSS catchment were distinct from the rest of the district. First, every year of HSS intervention was associated with an increase in the odds of vaccination in the HSS catchment between 1.18 (measles) and 1.43 (BCG), except for DTP. Unlike the rest of the district, children from wealthier households in the HSS catchment had lower odds of vaccination over time (OR of interaction ranging from 0.73 to 0.83), meaning that baseline economic inequalities were progressively reduced. However, the decrease in the odds of vaccination over time for more remote households in the HSS catchment (OR of interaction ranging from 0.72 to 0.84) effectively compensated the positive effect observed in the district as a whole, meaning that geographical inequalities were only reduced outside the HSS catchment. Full multivariate models that included all explanatory variables regardless of statistical significance (online supplemental table S5) had results consistent with those described here using reduced models.

In-sample predictions from these multivariate models for 2018 revealed stark differences for achieving international coverage targets depending on HSS support and population characteristics (figure 3). Overall, a 90% coverage (recommended coverage at the national level) could only be achieved for BCG, and just for populations who live in close proximity to a health centre with HSS support and who are among the wealthiest in the area. When the target is relaxed to 80% coverage (minimum coverage recommended for every district), there were some population subgroups for which this target could be achieved in the HSS catchment for every individual vaccine. The range of socioeconomic and geographical groups for which minimum coverage rates could be reached was much larger for BCG and polio than for DTP and measles (figure 3). Coverage targets for all recommended vaccines simultaneously (instead of each independently) could not be achieved for any population group. In areas outside of the HSS catchment, a 90% coverage was not achieved for any of the recommended vaccines or population subgroups. Only those in the top percentiles of wealth and proximity to a health centre achieved an 80% coverage for BCG vaccination without HSS support.

Timeliness of vaccination

Among the 786 children aged 12–59 months who had a vaccination card at the time of the interview, timeliness of vaccination varied widely depending on HSS support

Table 2 Determinants of vaccination coverage at the population level in Ifanadiana district, 2014–2018 (Generalized Linear Mixed Model (GLMM), multivariate results*)

Variable	BCG immunisation	Polio immunisation (third dose)	DTP immunisation (third dose)	Measles immunisation	All recommended vaccines
Immunisation coverage at baseline (intercept)	0.8 (0.73 to 0.86)	0.77 (0.71 to 0.83)	0.71 (0.62 to 0.78)	0.68 (0.61 to 0.75)	0.47 (0.38 to 0.56)
District-wide differences					
Baseline differences in HSS catchment vs control	0.6 (0.39 to 0.92)	–	1.65 (1.12 to 2.44)	–	–
Socioeconomic class (log of wealth score)	2.18 (1.51 to 3.15)	2.85 (1.92 to 4.23)	2.58 (1.75 to 3.8)	2.3 (1.6 to 3.32)	2.68 (1.84 to 3.91)
Distance to health centre (every 10 km)	0.22 (0.12 to 0.4)	0.3 (0.17 to 0.51)	0.31 (0.18 to 0.53)	0.53 (0.33 to 0.85)	0.35 (0.19 to 0.62)
Changes in the district					
Annual change	–	–	–	–	–
Annual changexsocioeconomic class	–	–	–	–	–
Annual changexdistance to health centre	1.31 (1.21 to 1.41)	1.31 (1.21 to 1.41)	1.23 (1.14 to 1.33)	–	1.17 (1.08 to 1.27)
Changes in the HSS catchment					
Change per year of HSS	1.43 (1.22 to 1.66)	1.19 (1.04 to 1.36)	–	1.18 (1.04 to 1.34)	1.22 (1.08 to 1.38)
Change per year of HSS×socioeconomic class	–	0.75 (0.6 to 0.95)	0.83 (0.67 to 1.03)	0.78 (0.63 to 0.97)	0.73 (0.59 to 0.9)
Change per year of HSS×distance to health centre	0.81 (0.65 to 1)	0.72 (0.58 to 0.9)	0.84 (0.73 to 0.96)	0.76 (0.62 to 0.91)	0.81 (0.66 to 1)

*Results are expressed as probabilities for the intercept and as OR with associated 95% CIs for all other variables. A sign '-' means that the variable was not part of the final reduced model for lack of statistical association.
DTP, diphtheria, tetanus and pertussis; HSS, health system strengthening.

and the vaccine considered (figure 4). Most children were vaccinated in the first month of life for BCG, at 4–5 months for the third dose of polio and DTP, and at 9–10 months for measles (figure 4A). Vaccination occurred later than recommended in national policies (see methods section) for many children, especially those outside the HSS catchment. As a result, the proportion of children vaccinated at the recommended age was higher in the HSS catchment, ranging between 58% for BCG and 44% for polio and DTP (figure 4B). In the rest of the district, this proportion was significantly lower and ranged between 49% for BCG and 22% for polio and DTP. Timeliness of vaccination improved between 2014 and 2018 in the HSS catchment for all vaccines except for BCG, while it only improved for measles in the rest of the district (online supplemental figure S1).

DISCUSSION

The COVID-19 pandemic has brought renewed attention to the benefits and challenges of ensuring global access to vaccines as the most effective means to reach herd immunity, halt epidemic spread and save countless lives.[57 58] For routine childhood immunisations, delivery strategies have not substantially changed in decades: vaccines are delivered by healthcare professionals, either at health facilities or through outreach activities in the form of vaccination campaigns. Understanding how these delivery strategies can be improved in order to achieve vaccination coverage targets is essential, especially in rural areas of the developing world where delivery is significantly more challenging due to the fragility of health systems and associated health budgets. Using a comprehensive dataset on childhood immunisations at both the health system and population levels in a rural district of Madagascar, we show here how strengthening local health systems can help improve key indicators of vaccination coverage, with different impacts on routine and outreach immunisations. The HSS intervention led to an increase in RI, resulting in higher vaccination coverage, a reduction in economic inequalities, and a higher proportion of timely vaccinations. Yet, these gains disproportionately benefited those who lived in closer proximity to health facilities. Lower contribution of outreach activities in the HSS catchment was associated with a persistence of inequalities in geographical coverage in the area, which prevented achieving international coverage targets for many population groups.

There is widespread agreement that RI should be the basis and the foundation of immunisation programmes, but questions remain on how to optimise the delicate balance between providing long-term support to RI and improving short-term access via outreach activities.[16 59]

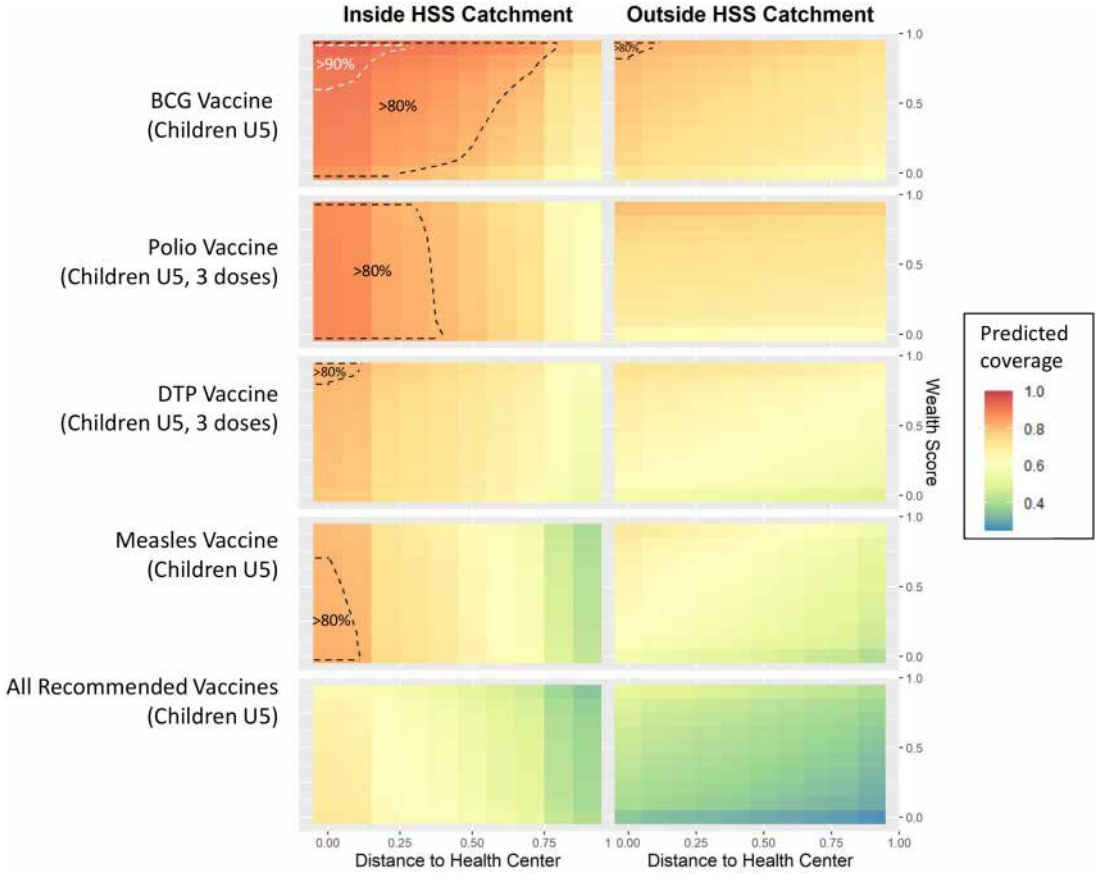

Figure 3 Predictions for achieving vaccination coverage targets for different population groups in Ifanadiana district. Graphs show in-sample predictions of vaccination coverage for the year 2018, estimated from models fitted with the cohort dataset (coefficients available in table 2). For this, vaccination coverage was estimated for every combination of household distance to health centre and wealth (split into deciles) in the HSS catchment and in the rest of the district, using the fixed effects of each model. Areas with predicted coverage greater than 90% or 80% are surrounded with white dashed lines or black dashed lines, respectively. DTP, health system strengthening; HSS, health system strengthening.

The multiplicity of barriers to accessing health facilities for populations in low-resource settings requires mass vaccination campaigns and other outreach activities to maintain or increase coverage, but these strategies can have, in turn, negative effects on the rates of RI.[13 28] For instance, RI in Madagascar decreased in the months after SIAs and VW, resulting in seasonal gaps in immunisation and delays from the recommended age of vaccination.[13] Here, we provide complementary insights: where RI improved due to ongoing HSS efforts, the contribution of outreach activities to overall vaccination coverage diminished, with mixed impacts on coverage inequalities. Timeliness of vaccination was better in the HSS catchment, with twice the proportion being vaccinated at the recommended age for polio, DTP and measles in the HSS catchment than in the rest of the district. Timely vaccination is key to ensuring that children are fully protected against common childhood illnesses by the time when they are most at risk, and can help prevent episodic outbreaks.[26]

We found that the HSS intervention was associated with a 20%–50% increase in the odds of monthly per capita immunisations, which resulted in a 20%–40% increase in the odds of coverage per year from 2014 to 2018, and a reduction in economic inequalities over time. This effect may seem counterintuitive, as immunisations are provided free of charge at health facilities across Madagascar as part of the national EPI. However, it has been widely reported that despite childhood vaccines being free of charge, children of poorer households frequently have lower vaccination coverage than their peers,[60–63] which is consistent with our findings. Seeking healthcare for healthy children may not be always be a priority for people living under severe poverty, especially given the disproportionate impact of the loss of income associated with seeking care, indirect transportation costs, and lower reported awareness of the long-term benefits of vaccination.[60–63] This may explain why BCG vaccination coverage decreased significantly as a function of distance to the health centre, as most deliveries in remote areas occur at home. The HSS intervention included, among others, renovations to health facilities, hiring of additional health staff, community sensitisation and expanded support for reproductive health, including deliveries in health facilities, antenatal and postnatal care, all of which could have improved the confidence on the health system

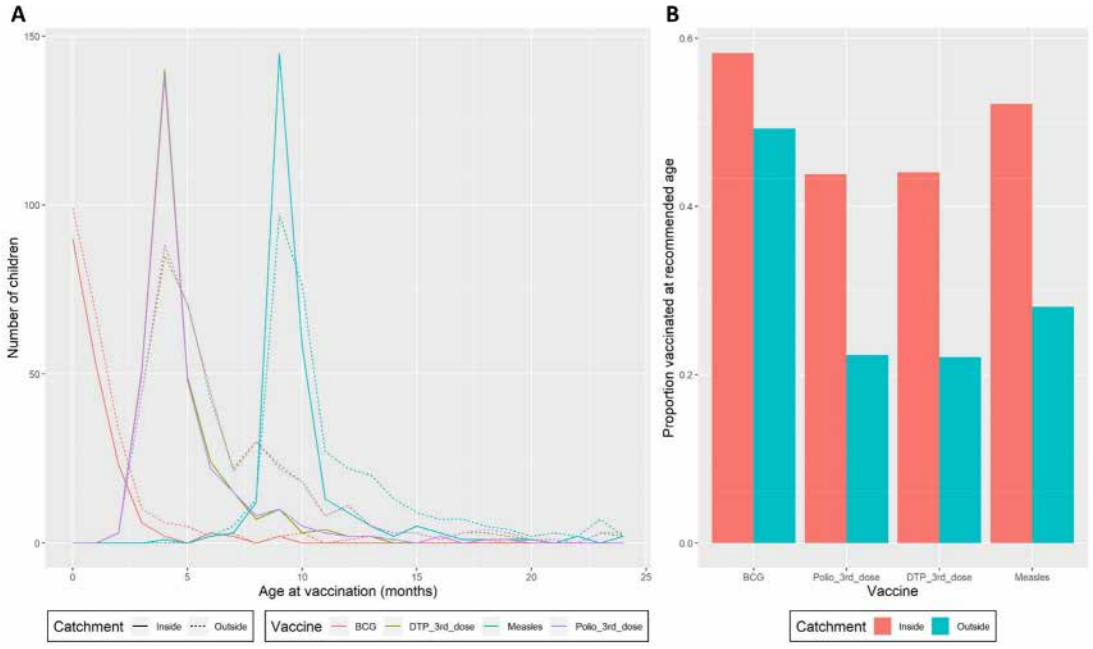

Figure 4 Timeliness of vaccination among children 12–59 months in Ifanadiana district. (A) Age of vaccine administration (in months) as reported in children's vaccination cards inside the HSS catchment (solid lines) and in the rest of the district (dashed lines), with colours representing each type of vaccine. (B) Proportion of children vaccinated at the recommended age for BCG (1st month), third dose of polio (4th month), third dose of DTP (4th month) and measles (9th month), as per the Madagascar Expanded Programme on Immunisation. DTP, diphtheria, tetanus and pertussis; HSS, health system strengthening.

and increased awareness, particularly among mothers of young children. In addition, the removal of user fees at health facilities, which resulted in a tripling of primary care utilisation for individuals of all ages over this period and significant increases in maternal health services,[55] could have had the indirect benefit of increasing health seeking for services that were already free of charge, as adults and mothers get more used to visiting health centres. An increase in perinatal health services could indeed explain why BCG vaccination coverage was consistently higher than measles coverage, since BCG is delivered right after birth as opposed to measles, which is delivered 9 months later. Health system approaches such as the one implemented in Ifanadiana are increasingly recognised as potential solutions to achieve, not only vaccination coverage targets, but also progress towards universal health coverage.[64 65]

Despite HSS efforts to support vaccination delivery at the community level during VW and other outreach activities, geographical inequalities in vaccination coverage persisted or even increased for certain vaccines in the HSS catchment, probably as a consequence of the higher contribution of facility-based immunisations to overall vaccination coverage in the area. Distance to healthcare facilities is a known determinant of low vaccination coverage,[60 66 67] especially in countries like Madagascar, where coverage is lower than average.[17] Outreach activities during VW and mass vaccination campaigns can be effective ways to reduce geographical inequalities,[21] and these took place in both the HSS catchment and the rest of the district. The higher contribution of outreach activities to overall vaccination coverage in the area of Ifanadiana not supported by the HSS intervention would explain why most of the gains in vaccination coverage were seen via a reduction of geographical inequalities over time (remote populations benefited more than populations living closer to health centres). However, previous modelling studies have shown that eliminating geographical inequalities alone will not achieve coverage targets across Africa, and that parallel increases in routine vaccination rates are necessary.[17] This is consistent with our results, where only certain population groups in the HSS catchment (those of higher socioeconomic level and living in proximity to health centres), but none in the rest of the district, actually reached international coverage targets required for herd immunity. Additional efforts are therefore necessary to sustain improvements in the district, including the geographical expansion of HSS efforts, and a particular focus on supporting outreach activities in the HSS catchment (eg, more frequent vaccination campaigns, routine expeditions by mobile teams).

Our study had several limitations. First, we used official MoPH data on population size for children aged 12–23 months in our analysis of per capita immunisations at health centres. These are notoriously inaccurate and can lead to estimated coverage rates above 100%, which would be the case in our setting if we had used annualised rates. This is unlikely to have affected our analysis unless inaccuracies in population data were highly structured across health centres (much overestimated in some and underestimated in others). The consistency between health system and cohort results suggests that there was limited bias in the analyses of per capita immunisations. Second, less than one-third of the children studied in the

cohort had a vaccination card at the time of the interview, so their vaccination status (and therefore estimates of coverage) depended largely on the mother's report. Although potentially flawed due to recall bias, vaccination coverage figures used by most international organisations and national governments are based on surveys (DHS, MICS, etc) that use the same methods, and the proportion of children with vaccination cards was not lower here than in other settings.[68] Third, our analysis of vaccination timeliness used exclusively children with vaccination cards and we observed that this group was significantly wealthier and closer to health facilities than children without vaccination cards (online supplemental table S3), so timeliness results may not be generalisable to the whole district population. Fourth, although we account for baseline differences between the two areas in our models, the HSS catchment had significantly better socioeconomic indicators than the rest of the district,[44] which could have impacted the positive results observed in the HSS catchment over time. Finally, although the IHOPE cohort includes over 8000 individuals, the sample size for children aged 12–23 months is relatively low, which precludes the robust estimation of vaccination coverage predictors with complex statistical models. For this reason, we expanded the age range of the cohort statistical analyses to children aged 12–59 months. This could have had an impact in the interpretation of results if trends observed for children 12–59 months were greatly different from those in children 12–23 months.

In conclusion, our study shows that strengthening local health systems can help improve vaccination coverage and timeliness of immunisation in rural, low-resource settings, even when those interventions do not target specifically vaccine improvements themselves. By increasing the contribution of RI over other immunisation strategies such as VW or mass campaigns, the intervention helped reduce economic inequalities in vaccination coverage, but failed to reduce geographical inequalities. Overall, the target of 90% immunisation coverage was not achieved for any vaccine, but many populations in the HSS intervention area achieved immunisation levels above 80%. Explicit efforts are necessary in areas undergoing HSS to vaccinate children in remote areas so that immunisation goals can be reached.

Author affiliations
[1]Sciences & Ingénierie, Sorbonne Universite, Paris, France
[2]UMR 224 MIVEGEC, Univ. Montpellier-CNRS-IRD, Montpellier, France
[3]NGO PIVOT, Ranomafana, Madagascar
[4]Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, USA
[5]National Institute of Statistics, Antananarivo, Madagascar
[6]Ministry of Public Health, Antananarivo, Madagascar
[7]Dept of Ecology and Evol. Biology, Princeton University, Princeton, New Jersey, USA
[8]Universidad Nacional Autónoma de México, Coyoacan, Distrito Federal, Mexico

Twitter C Jessica Metcalf @CJEMetcalf

Acknowledgements The authors acknowledge the contributions and support Herrnstein Family Foundation, and Benjamin Andriamihaja. They are grateful to all of the staff at PIVOT for their field support and their remarkable work in strengthening the health system in Ifanadiana. Thanks are due to the Madagascar Ministry of Health, at both the district and the central levels, for their continuous support and valuable insights. The authors also thank the Institut National de la Statistique (INSTAT) field teams for their involvement in the district wide population survey. Special thanks to Amy Wesolowski for insightful discussions.

Contributors Conceived and designed the experiments: ER, AG, ACM, MHB and CJM. Collected the data: BRaz and MR. Performed the analysis: ER and AG. Wrote the initial draft of the manuscript: ER and AG. Revised the manuscript and accepted it in its final form: ER, MHB, ACM, FAI, LC, BRat, FHR, KEF, RJLR, GC, BRat, FR, MR, EMR-F, AR, CJM, BRo and AG. Act as guarrantor of the study: ER and AG.

Funding This study was funded by Institut de Recherche pour le Développement (Allocation de Recherche pour une Thèse au Sud (ARTS)); Herrnstein Family Foundation; NGO PIVOT Madagascar.

Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s)

Ethics approval This study was approved by—Madagascar National Ethics Committee (041/MSANP/SG/AGMED/CERBM)—The Harvard Medical School Institutional Review Board (IRB16-0347).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data used in this study are available from the corresponding author on request.

ORCID iDs
C Jessica Metcalf http://orcid.org/0000-0003-3166-7521
Andres Garchitorena http://orcid.org/0000-0001-6225-5226

REFERENCES

1 Greenwood B. The contribution of vaccination to global health: past, present and future. *Philos Trans R Soc Lond B Biol Sci* 2014;369:20130433.
2 Doherty M, Buchy P, Standaert B, *et al*. Vaccine impact: benefits for human health. *Vaccine* 2016;34:6707–14.
3 Brugha R, Starling M, Walt G. GAVI, the first steps: lessons for the global fund. *Lancet* 2002;359:435–8.
4 GAVI. "Gavi's strategy," The vaccine Alliance, 2015. Available: http://www.gavi.org/about/strategy/
5 Unicef and World Health Organization,. Progress and Challenges with Achieving Universal Immunization Coverage : 2015 Estimates of Immunization Coverage 2018.
6 Zerhouni E. GAVI, the vaccine alliance. *Cell* 2019;179:13–17.
7 Lee LA, Franzel L, Atwell J, *et al*. The estimated mortality impact of vaccinations forecast to be administered during 2011-2020 in 73 countries supported by the GAVI alliance. *Vaccine* 2013;31 Suppl 2:B61–72.
8 Organisation Mondiale de la Santé. Le plan D ' action mondial pour les vaccins 2013:1–8.
9 World Health Organization. *Global vaccine action plan*. Geneva, Switzerland, 2013.
10 World Health Organization. *A guide to increasing coverage and equity in all communities in the African region 20*, 2017.
11 Rainey JJ, Watkins M, Ryman TK, *et al*. Reasons related to non-vaccination and under-vaccination of children in low and middle income countries: findings from a systematic review of the published literature, 1999-2009. *Vaccine* 2011;29:8215–21.

12 Luquero FJ, Pham-Orsetti H, Cummings DAT, *et al*. A long-lasting measles epidemic in Maroua, Cameroon 2008-2009: mass vaccination as response to the epidemic. *J Infect Dis* 2011;204(Suppl 1):S243–51.
13 Mensah K, Heraud JM, Takahashi S, *et al*. Seasonal gaps in measles vaccination coverage in Madagascar. *Vaccine* 2019;37:2511–9.
14 Cutts FT, Lessler J, Metcalf CJE. Measles elimination: progress, challenges and implications for rubella control. *Expert Rev Vaccines* 2013;12:917–32.
15 GAVI. *Gavi strategy 2021-2025 one-pager*, 2021.
16 Duclos P, Okwo-Bele J-M, Gacic-Dobo M, *et al*. Global immunization: status, progress, challenges and future. *BMC Int Health Hum Rights* 2009;9 Suppl 1:S2.
17 Metcalf CJE, Tatem A, Bjornstad ON, *et al*. Transport networks and inequities in vaccination: remoteness shapes measles vaccine coverage and prospects for elimination across Africa. *Epidemiol Infect* 2015;143:1457–66.
18 Utazi CE, Thorley J, Alegana VA, *et al*. High resolution age-structured mapping of childhood vaccination coverage in low and middle income countries. *Vaccine* 2018;36:1583–91.
19 Byberg S, Thysen SM, Rodrigues A, *et al*. A general measles vaccination campaign in urban Guinea-Bissau: comparing child mortality among participants and non-participants. *Vaccine* 2017;35:33–9.
20 Bonu S, Rani M, Baker TD. The impact of the National polio immunization campaign on levels and equity in immunization coverage: evidence from rural North India. *Soc Sci Med* 2003;57:1807–19.
21 Portnoy A, Jit M, Helleringer S, *et al*. Comparative Distributional impact of routine immunization and supplementary immunization activities in delivery of measles vaccine in low- and middle-income countries. *Value Health* 2020;23:891–7.
22 Wang L, Liu Z, Zhang X. Global dynamics for an age-structured epidemic model with media impact and incomplete vaccination. *Nonlinear Anal Real World Appl* 2016;32:136–58.
23 Barron PM, Buch E, Behr G, *et al*. Mass immunisation campaigns--do they solve the problem? *S Afr Med J* 1987;72:321–2.
24 Metcalf CJE, Klepac P, Ferrari M, *et al*. Modelling the first dose of measles vaccination: the role of maternal immunity, demographic factors, and delivery systems. *Epidemiol Infect* 2011;139:265–74.
25 Nguipdop-Djomo P, Heldal E, Rodrigues LC, *et al*. Duration of BCG protection against tuberculosis and change in effectiveness with time since vaccination in Norway: a retrospective population-based cohort study. *Lancet Infect Dis* 2016;16:219–26.
26 Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. *Lancet* 2009;373:1543–9.
27 Miyahara R, Jasseh M, Gomez P, *et al*. Barriers to timely administration of birth dose vaccines in the Gambia, West Africa. *Vaccine* 2016;34:3335–41.
28 Chakrabarti A, Grépin KA, Helleringer S. The impact of supplementary immunization activities on routine vaccination coverage: an instrumental variable analysis in five low-income countries. *PLoS One* 2019;14:e0212049–11.
29 Wallace AS, Bohara R, Stewart S, *et al*. Impact of an intervention to use a measles, rubella, and polio mass vaccination campaign to strengthen routine immunization services in Nepa. *J Infect Dis* 2017;216:S280–6.
30 Saliou P. Le programme élargi de vaccination (PEV) : origine et évolution, Developpement et Santé, 2009. Available: https://devsante.org/articles/le-programme-elargi-de-vaccination-pev-origine-et-evolution
31 Pierrette RJ. Perception des parents des enfants âgés de 12 59 mois sur La vaccination Ambohipo-Ambolonkandrina.
32 Masquelier B, Waltisperger D, Ralijaona O, *et al*. The epidemiological transition in Antananarivo, Madagascar: an assessment based on death registers (1900-2012). *Glob Health Action* 2014;7:23237.
33 USAID. Implication de la commune dans la santé des mères et enfants Madagascar:1–21.
34 Organisation Mondiale de la Santé,. Madagascar célèbre la Semaine Mondiale de la Vaccination (SMV) couplée la Semaine de la Santé de la Mère et de l'Enfant (SSME), 23 au 27 Avril 2012, OMS, 2012. Available: https://www.afro.who.int/fr/news/madagascar-celebre-la-semaine-mondiale-de-la-vaccination-smv-couplee-la-semaine-de-la-sante-de
35 Winter AK, Wesolowski AP, Mensah KJ, *et al*. Revealing measles outbreak risk with a nested immunoglobulin G serosurvey in Madagascar. *Am J Epidemiol* 2018;187:2219–26.
36 Lessler J, Metcalf CJE, Cutts FT, *et al*. Impact on epidemic measles of vaccination campaigns triggered by disease outbreaks or serosurveys: a modeling study. *PLoS Med* 2016;13:e1002144.
37 INSTAT. *Madagascar Enquête PAR grappes indicateurs*, 2019.
38 GAVI. *Rapport de L ' évaluation conjointe (JA) 2018*, 2020.
39 Organisation Mondiale de la Santé,. Rougeole - Madagascar, *OMS*, 2019. Available: https://www.who.int/csr/don/17-january-2019-measles-madagascar/fr/
40 Unicef and World Health Organization. *Progress and Challenges with Achieving Universal Immunization Coverage : 2019 Estimates of National Immunization Coverage*, 2019: 1–18.
41 Finnegan KE*et al*. Rapid response to a measles outbreak in Ifanadiana district, Madagascar. *medRxiv* 2020:1–7.
42 Bonds MH*et al*. Advancing a science for sustaining health: establishing a model health district in Madagascar 2017:1–7.
43 Garchitorena A, Miller AC, Cordier LF, *et al*. District-level health system strengthening for universal health coverage: evidence from a longitudinal cohort study in rural Madagascar, 2014-2018. *BMJ Glob Health* 2020;5:e003647.
44 Miller AC, Ramananjato RH, Garchitorena A, *et al*. Baseline population health conditions ahead of a health system strengthening program in rural Madagascar. *Glob Health Action* 2017;10:1329961.
45 Ezran C, Bonds MH, Miller AC, *et al*. Assessing trends in the content of maternal and child care following a health system strengthening initiative in rural Madagascar: a longitudinal cohort study. *PLoS Med* 2019;16:e1002869.
46 Cordier LF, Kalaris K, Rakotonanahary RJL, *et al*. Networks of care in rural Madagascar for achieving universal health coverage in Ifanadiana district. *Health Syst Reform* 2020;6:e1841437.
47 M. de la santé publique Madagascar. *Number of vaccinated children in the district of Ifanadiana: between 2014 and 2018*, 2018.
48 Garchitorena A, Miller AC, Cordier LF, *et al*. In Madagascar, use of health care services increased when fees were removed: lessons for universal health coverage. *Health Aff* 2017;36:1443–51.
49 Miller AC, Garchitorena A, Rabeza V, *et al*. Cohort profile: Ifanadiana health outcomes and prosperity longitudinal evaluation (IHOPE). *Int J Epidemiol* 2018;47:1394–5.
50 USAID. *Survey organization manual demographic and health surveys methodology*, 2013.
51 Brown DW, Burton AH, Feeney G, *et al*. Avoiding the Will O' the Wisp: Challenges in Measuring High Levels of Immunization Coverage with Precision. *World J Vaccines* 2014;04:97–9.
52 Stashko LA, Gacic-Dobo M, Dumolard LB, *et al*. Assessing the quality and accuracy of national immunization program reported target population estimates from 2000 to 2016. *PLoS One* 2019;14:e0216933.
53 Bharti N, Djibo A, Tatem AJ, *et al*. Measuring populations to improve vaccination coverage. *Sci Rep* 2016;5:1–10.
54 Ihantamalala FA, Herbreteau V, Révillion C, *et al*. Improving geographical accessibility modeling for operational use by local health actors. *Int J Health Geogr* 2020;19:1–15.
55 Garchitorena A, Miller AC, Cordier LF, *et al*. Early changes in intervention coverage and mortality rates following the implementation of an integrated health system intervention in Madagascar. *BMJ Glob Health* 2018;3:e000762–12.
56 Victora CG, Barros AJD, França GVA, *et al*. The contribution of poor and rural populations to national trends in reproductive, maternal, newborn, and child health coverage: analyses of cross-sectional surveys from 64 countries. *Lancet Glob Health* 2017;5:e402–7.
57 Wouters OJ, Shadlen KC, Salcher-Konrad M, *et al*. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. *Lancet* 2021;397:1023–34.
58 Wang W, Wu Q, Yang J, *et al*. Global, regional, and national estimates of target population sizes for covid-19 vaccination: descriptive study. *BMJ* 2020;371:m4704.
59 Sodha SV, Dietz V. Strengthening routine immunization systems to improve global vaccination coverage. *Br Med Bull* 2015;113:5–14.
60 de Figueiredo A, Johnston IG, Smith DMD, *et al*. Forecasted trends in vaccination coverage and correlations with socioeconomic factors: a global time-series analysis over 30 years. *Lancet Glob Health* 2016;4:e726–35.
61 Panda BK. Temporal Trend and Inequality in Immunization Coverage in India. In: *Public Health in Developing Countries - Challenges and Opportunities*, 2020.
62 Egondi T, Oyolola M, Mutua MK, *et al*. Determinants of immunization inequality among urban poor children: evidence from Nairobi's informal settlements. *Int J Equity Health* 2015;14:24.
63 Kien VD, Van Minh H, Giang KB, *et al*. Trends in childhood measles vaccination highlight socioeconomic inequalities in Vietnam. *Int J Public Health* 2017;62:41–9.
64 Lahariya C. "Health system approach" for improving immunization program performance. *J Family Med Prim Care* 2015;4:487.
65 Gera R1*et al*. Implementation of 'health systems approach' to improve vaccination at birth in institutional deliveries at public health

facilities; experience from six states of India. *J. Fam. Med. Prim. Care* 2017;6:169–70.
66 Jani JV, De Schacht C, Jani IV, *et al*. Risk factors for incomplete vaccination and missed opportunity for immunization in rural Mozambique. *BMC Public Health* 2008;8:1–7.
67 Blanford JI, Kumar S, Luo W, *et al*. It's a long, long walk: accessibility to hospitals, maternity and integrated health centers in niger. *Int J Health Geogr* 2012;11:24.
68 Wagner AL. The use and significance of vaccination cards. *Hum Vaccin Immunother* 2019;15:2844–6.